(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
6 June 2002 (06.06.2002)

PCT

(10) International Publication Number
WO 02/44383 A1

(51) International Patent Classification[7]: C12N 15/31, C12R 1:225)

(21) International Application Number: PCT/NZ01/00286

(22) International Filing Date:
28 November 2001 (28.11.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
09/724,623 28 November 2000 (28.11.2000) US

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(81) Designated States *(national)*: AE, AG, AL, AM, AT, AT (utility model), AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, CZ (utility model), DE, DE (utility model), DK, DK (utility model), DM, DZ, EC, EE, EE (utility model), ES, FI, FI (utility model), GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SK (utility model), SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 02/44383 A1

(54) Title: LACTOBACILLUS RHAMNOSUS POLYNUCLEOTIDES, POLYPEPTIDES AND METHODS FOR USING THEM

(57) Abstract: Novel polynucleotides isolated from *Lactobacillus rhamnosus*, as well as probes and primers, genetic constructs comprising the polynucleotides, biological materials, including plants, microorganisms and multicellular organisms incorporating the polynucleotides, polypeptides expressed by the polynucleotides, and methods for using the polynucleotides and polypeptides are disclosed.

LACTOBACILLUS RHAMNOSUS POLYNUCLEOTIDES, POLYPEPTIDES AND METHODS FOR USING THEM

Technical Field of the Invention

This invention relates to polynucleotides isolated from lactic acid bacteria, namely *Lactobacillus rhamnosus*, including partial and extended sequences, as well as to probes and primers specific to the polynucleotides; DNA constructs comprising the polynucleotides; biological materials, including plants, microorganisms and multicellular organisms incorporating the polynucleotides; polypeptides expressed by the polynucleotides; and methods for using the polynucleotides and polypeptides.

Background of the Invention

The present invention relates to polynucleotides isolated from a specific strain of lactic acid bacteria, namely *Lactobacillus rhamnosus* HN001 (*L. rhamnosus* HN001). Lactic acid bacteria, and their enzymes, are the major determinants of flavor and fermentation characteristics in fermented dairy products, such as cheese and yogurt. Flavors are produced through the action of bacteria and their enzymes on proteins, carbohydrates and lipids.

Lactobacillus rhamnosus strain HN001 are heterofermentative bacteria that are Gram positive, non-motile, non-spore forming, catalase negative, facultative anaerobic rods exhibiting an optimal growth temperature of 37±1°C and an optimum pH of 6.0 – 6.5. Experimental studies demonstrated that dietary supplementation with *Lactobacillus rhamnosus* strain HN001 induced a sustained enhancement in several aspects of both natural and acquired immunity (*See* PCT International Publication No. WO 99/10476). In addition, *L. rhamnosus* HN001, and certain other Gram-positive bacteria can specifically and directly modulate human and animal health (See, for example, Tannock *et al.*, *Applied Environ. Microbiol.* 66:2578-2588, 2000; Gill *et al.*, *Brit. J. Nutrition* 83:167-176; Quan Shu *et al.*, *Food and Chem. Toxicol.* 38:153-161, 2000; Quan Shu *et al.*, *Intl. J. Food Microbiol.* 56:87-96, 2000; Quan Shu *et al.*, *Intl. Dairy J.* 9:831-836, 1999; Prasad *et al.*, *Intl. Dairy J.* 8:993-1002, 1998; Sanders and Huis in't Veld, *Antonie van Leeuwenhoek* 76:293-315, 1999; Salminen *et al.*, 1998. *In*: Lactic Acid Bacteria, Salminen S and von Wright A (eds)., Marcel Dekker Inc, New York, Basel, Hong Kong, pp. 211-253; Delcour *et al.*, *Antonie van Leeuwenhoek* 76:159-184, 1999; Blum *et al.*, *Antonie van Leeuwenhoek* 76:199-205, 1999;

Yasui *et al.*, *Antonie van Leeuwenhoek* 76:383-389, 1999; Hirayama and Rafter, *Antonie van Leeuwenhoek* 76:391-394, 1999; Ouwehand, 1998. *In*: Lactic Acid Bacteria, Salminen S and von Wright A (eds)., Marcel Dekker Inc, New York, Basel, Hong Kong, pp. 139-159; Isolauri *et al.*, S 1998. *In*: Lactic Acid Bacteria, Salminen S and von Wright A (eds)., Marcel Dekker Inc, New York, Basel, Hong Kong, pp. 255-268; Lichtenstein and Goldin, 1998. *In*: Lactic Acid Bacteria, Salminen S and von Wright A (eds)., Marcel Dekker Inc, New York, Basel, Hong Kong, pp. 269-277; El-Nezami and Ahokas, 1998. *In*: Lactic Acid Bacteria, Salminen S and von Wright A (eds)., Marcel Dekker Inc, New York, Basel, Hong Kong, pp. 629-367; Nousianen *et al.*, 1998. *In*: Lactic Acid Bacteria, Salminen S and von Wright A (eds)., Marcel Dekker Inc, New York, Basel, Hong Kong, pp. 437-473; Meisel and Bockelmann, *Antonie van Leeuwenhoek* 76:207-215, 1999; Christensen *et al.*, *Antonie van Leeuwenhoek* 76:217-246, 1999; Dunne *et al.*, *Antonie van Leeuwenhoek* 76:279-292, 1999). Beneficial health effects attributed to these bacteria include the following:

Increased resistance to enteric pathogens and anti-infection activity, including treatment of rotavirus infection and infantile diarrhea – due to increases in antibody production caused by an adjuvant effect, increased resistance to pathogen colonization; alteration of intestinal conditions, such as pH; and the presence of specific antibacterial substances, such as bacteriocins and organic acids.

Aid in lactose digestion – due to lactose degradation by bacterial lactase enzymes (such as beta-galactosidase) that act in the small intestine.

Anti-cancer (in particular anti-colon cancer) and anti-mutagenesis activities – due to anti-mutagenic activity; alteration of procancerous enzymatic activity of colonic microbes; reduction of the carcinogenic enzymes azoreductase, beta-glucuronidase and nitroreductase in the gut and/or faeces; stimulation of immune function; positive influence on bile salt concentration; and antioxidant effects.

Liver cancer reduction – due to aflatoxin detoxification and inhibition of mould growth.

Reduction of small bowel bacterial overgrowth – due to antibacterial activity; and decrease in toxic metabolite production from overgrowth flora.

Immune system modulation and treatment of autoimmune disorders and allergies – due to enhancement of non-specific and antigen-specific defence against infection and tumors; enhanced mucosal immunity; adjuvant effect in antigen-specific immune responses; and regulation of Th1/Th2 cells and production of cytokines.

Treatment of allergic responses to foods – due to prevention of antigen translocation into blood stream and modulation of allergenic factors in food.

Reduction of blood lipids and prevention of heart disease – due to assimilation of cholesterol by bacteria; hydrolysis of bile salts; and antioxidative effects.

Antihypertensive effect - bacterial protease or peptidase action on milk peptides produces antihypertensive peptides. Cell wall components act as ACE inhibitors

Prevention and treatment of urogenital infections – due to adhesion to urinary and vaginal tract cells resulting in competitive exclusion; and production of antibacterial substances (acids, hydrogen peroxide and biosurfactants).

Treatment of inflammatory bowel disorder and irritable bowel syndrome – due to immuno-modulation; increased resistance to pathogen colonization; alteration of intestinal conditions such as pH; production of specific antibacterial substances such as bacteriocins, organic acids and hydrogen peroxide and biosurfactants; and competitive exclusion.

Modulation of infective endocarditis – due to fibronectin receptor-mediated platelet aggregation associated with *Lactobacillus* sepsis.

Prevention and treatment of *Helicobacter pylori* infection – due to competitive colonization and antibacterial effect.

Prevention and treatment of hepatic encephalopathy – due to inhibition and/or exclusion of urease-producing gut flora.

Improved protein and carbohydrate utilisation and conversion – due to production of beneficial products by bacterial action on proteins and carbohydrates.

Other beneficial health effects associated with *L. rhamnosus* and its components include: improved nutrition; regulation of colonocyte proliferation and differentiation; improved lignan and isoflavone metabolism; reduced mucosal permeability; detoxification of carcinogens and other harmful compounds; relief of constipation and diarrhea; and vitamin synthesis, in particular folate.

Peptidases are enzymes that break the peptide bonds linking the amino group of one amino acid with the carboxy group (acid group) of an adjacent amino acid in a peptide chain. The bonds are broken in a hydrolytic reaction. There is a large family of peptidase enzymes that are defined by their specificity for the particular peptides bonds that they cleave (Barrett A J, Rawlings N D and Woessner J F (Eds.) 1998. *Handbook of proteolytic enzymes*. Academic Press, London, UK). The two main families are exopeptidases and endopeptidases.

Exopeptidases cleave amino acids from the N- or C- terminus of a peptide chain, releasing free amino acids or short (di- and tripeptides). Different types of exopeptidases include:

- Aminopeptidases - release a free amino acid from the N-terminus of a peptide chain;
- dipeptidyl-peptidase (also known as dipeptidyl-aminopeptidases) - release a dipeptide from the N-terminus of a peptide chain;
- tripeptidyl-peptidases (also known as tripeptidyl-aminopeptidases) - release a tripeptide from the N-terminus of a peptide chain);
- carboxypeptidases - release a free amino acid from the C-terminus of a peptide chain;
- peptidyl-dipeptidase - release a dipeptide from the C-terminus of a peptide chain;
- dipeptidases - release two free amino acids from a dipeptide; and
- tripeptidases - release a free amino acid and a dipeptide from a tripeptide.

Endopeptidases hydrolyze peptide bonds internally within a peptide and are classified on the basis of their mode of catalysis:

- serine-endopeptidases – depend on serine (or threonine) as the nucleophile in the catalytic reaction;
- cysteine-endopeptidases - depend on the sulphydryl group of cysteine as the nucleophile in the catalytic reaction;
- aspartic-endopeptidases - contain aspartate residues that act as ligands for an activated water molecule which acts as the nucleophile in the catalytic reaction; and
- metallo-endopeptidases - contain one or more divalent metal ions that activate the water molecule that acts as the nucleophile in the catalytic reaction.

Peptidases are important enzymes in the process of cheese ripening and the development of cheese flavor. The hydrolysis of milk caseins in cheese results in textural changes and the development of cheese flavors. The raft of proteolytic enzymes that cause this hydrolysis come from the lactic acid bacteria that are bound up in the cheese – either starter cultures that grow up during the manufacture of the cheese, or adventitious and adjunct non-starter lactic acid bacteria that grow in the cheese as it ripens (Law Haandrikman, *Int. Dairy J.* 7:1-11, 1997).

Many other enzymes can also influence dairy product flavor, and functional and textural characteristics, as well as influencing the fermentation characteristics of the bacteria, such as speed of growth, acid production and survival (Urbach, *Int. Dairy J.* 5:877-890, 1995; Johnson and Somkuti, *Biotech. Appl. Biochem.* 13:196-204, 1991; El Soda and Pandian, *J. Dairy Sci.* 74:2317-2362, 1991; Fox *et al,*. In Cheese: chemistry, physics and microbiology. Volume 1, General aspects, 2nd edition, P Fox (ed) Chapman and Hall, London; Christensen *et al., Antonie van Leeuwenhoek* 76:217-246, 1999; Stingle *et al., J. Bacteriol.* 20:6624-6360, 1999; Stingle *et al., Mol. Microbiol.* 32:1287-1295, 1999; Lemoine *et al., Appl. Environ. Microbiol.* 63:1512-6218, 1997). Enzymes influencing specific characteristics and/or functions include the following:

- **Lysis of cells.** These enzymes are mostly cell wall hydrolases, including amidases; muramidases; lysozymes, including N-acetyl muramidase; muramidase; N-acetylglucosaminidase; and N-acetylmuramoyl-L-alanine amidase. DEAD-box helicase proteins also influence autolysis.

- **Carbohydrate utilization.** Lactose, citrate and diacetyl metabolism, and alcohol metabolism are particularly important. The enzymes involved include beta-galactosidase, lactate dehydrogenase, citrate lyase, citrate permease, 2,3 butanediol dehydrogenase (acetoin reductase), acetolactate decaboxylase, acetolactate synthase, pyruvate decarboxylase, pyruvate formate lyase, diacetyl synthase, diacetyl reductase, alcohol decarboxylase, lactate dehydrogenase, pyruvate dehydrogenase, and aldehyde dehydrogenase.

- **Lipid degradation, modification or synthesis.** Enzymes involved include lipases, esterases, phospholipases, serine hydrolases, desaturases, and linoleate isomerase.

- **Polysaccharide synthesis.** Polysaccharides are important not only for potential immune enhancement and adhesion activity but are important for the texture of fermented dairy products. The enzymes involved are a series of glucosyl transferases, including beta-(1-3) glucosyl transferase, alpha-N acetylgalactosaminyl transferase, phosphogalactosyl transferase, alpha-glycosyl transferase, UDP-N-acetylglucosamine C4 epimerase and UDP-N-acetylglucosamine transferase.

- **Amino acid degradation.** Enzymes include glutamate dehydrogenase, aminotransferases, amino acid decarboxylases, and enzymes involved in sulphur amino acid degradation including cystothione beta-lyase.

Sequencing of the genomes, or portions of the genomes, of numerous organisms, including humans, animals, microorganisms and various plant varieties, has been and is being carried out on a large scale. Polynucleotides identified using sequencing techniques may be partial or full-length genes, and may contain open reading frames, or portions of open reading frames, that encode polypeptides. Putative polypeptides may be identified based on polynucleotide sequences and further characterized. The sequencing data relating to polynucleotides thus represents valuable and useful information.

Polynucleotides and polypeptides may be analyzed for varying degrees of novelty by comparing identified sequences to sequences published in various public domain databases, such as EMBL. Newly identified polynucleotides and corresponding putative polypeptides may also be compared to polynucleotides and polypeptides contained in public domain

information to ascertain homology to known polynucleotides and polypeptides. In this way, the degree of similarity, identity or homology of polynucleotides and polypeptides having an unknown function may be determined relative to polynucleotides and polypeptides having known functions.

Information relating to the sequences of isolated polynucleotides may be used in a variety of ways. Specified polynucleotides having a particular sequence may be isolated, or synthesized, for use in *in vivo* or *in vitro* experimentation as probes or primers. Alternatively, collections of sequences of isolated polynucleotides may be stored using magnetic or optical storage medium and analyzed or manipulated using computer hardware and software, as well as other types of tools.

Summary of the Invention

The present invention provides isolated polynucleotides comprising a sequence selected from the group consisting of: (a) sequences identified in the attached Sequence Listing as SEQ ID NOS: 1-59; (b) variants of those sequences; (c) extended sequences comprising the sequences set out in SEQ ID NOS: 1-59, and their variants; and (d) sequences comprising at least a specified number of contiguous residues of a sequence of SEQ ID NOS: 1-59 (x-mers). Oligonucleotide probes and primers corresponding to the sequences set out in SEQ ID NOS: 1-59 and their variants are also provided. All of these polynucleotides and oligonucleotide probes and primers are collectively referred to herein, as "polynucleotides of the present invention."

The polynucleotide sequences identified as SEQ ID NOS: 1-59 were derived from a microbial source, namely from fragmented genomic DNA of *Lactobacillus rhamnosus*, strain HN001, described in PCT International Publication No. WO 99/10476. *Lactobacillus rhamnosus* strain HN001 are heterofermentative bacteria that are Gram positive, non-motile, non-spore forming, catalase negative, facultative anaerobic rods exhibiting an optimal growth temperature of 37±1°C and an optimum pH of 6.0 – 6.5. Experimental studies demonstrated that dietary supplementation with *Lactobacillus rhamnosus* strain HN001 induced a sustained enhancement in several aspects of both natural and acquired immunity. A biologically pure culture of *Lactobacillus rhamnosus* strain HN001 was deposited at the Australian Government Analytical Laboratories (AGAL), The New South Wales Regional Laboratory, 1 Suakin Street, Pymble, NSW 2073, Australia, as Deposit No. NM97/09514, dated 18 August 1997.

The polynucleotides identified as SEQ ID NOS: 1-59 were isolated from *Lactobacillus rhamnosus* genomic DNA clones and represent sequences that are present in the cells from which the DNA was prepared. The sequence information may be used to identify and isolate, or synthesize, DNA molecules such as promoters, DNA-binding elements, open reading frames or full-length genes, that then can be used as expressible or otherwise functional DNA in transgenic organisms. Similarly, RNA sequences, reverse sequences, complementary sequences, antisense sequences and the like, corresponding to the polynucleotides of the present invention, may be routinely ascertained and obtained using the polynucleotides identified as SEQ ID NOS: 1-59.

Many of the polynucleotide sequences disclosed herein are "full-length" sequences, in that they represent a full-length gene encoding a full-length polypeptide and confirm an open reading frame. Some of the polynucleotides are partial length, in that they do not represent a full-length gene. Such partial length sequences may be extended as described herein to obtain the full-length sequences. RNA sequences, reverse sequences, complementary sequences, antisense sequences and the like, corresponding to the polynucleotides of the present invention, may be routinely ascertained and obtained using the polynucleotides identified as SEQ ID NOS: 1-59.

The present invention further provides isolated polypeptides encoded, or partially encoded by the polynucleotides disclosed herein. In certain specific embodiments, the polypeptides of the present invention comprise a sequence selected from the group consisting of sequences identified as SEQ ID NO: 62-120, and variants thereof. Polypeptides encoded by the polynucleotides of the present invention may be expressed and used in various assays to determine their biological activity. Such polypeptides may be used to raise antibodies, to isolate corresponding interacting proteins or other compounds, and to quantitatively determine levels of interacting proteins or other compounds. The polypeptides of the present invention may also be used as nutritional additives and as additives in dairy processing and fermentation processing. Several polypeptides of the present invention also have human and animal health related benefits.

Genetic constructs comprising the inventive polynucleotides are also provided, together with transgenic host cells comprising such constructs and transgenic organisms, such as microbes, comprising such cells. Desired attributes may be produced in food, such as dairy (including milk protein hydrolysates and cheese), in living organisms and in non-food systems, by directed activity or directed suppression of activity of the appropriate enzyme.

Directed activity of an enzyme may be achieved by introducing an appropriate polynucleotide or polypeptide to a bacterial strain (including strain HN001, or starter cultures), or by administering an enzyme preparation.

The present invention also contemplates methods for modulating the polynucleotide and/or polypeptide content and composition of an organism, such methods involving stably incorporating into the genome of the organism a genetic construct comprising a polynucleotide of the present invention. . Such modulation may involve up regulating or down regulating expression from one or more polynucleotides of the present invention. Up regulation may be accomplished, for example, by providing multiple gene copies, modulating expression by modifying regulatory elements or the like. Similarly, down regulation may be accomplished using known antisense and gene silencing techniques. In one embodiment, the target organism is a microbe, preferably a microbe used in fermentation, more preferably a microbe of the genus *Lactobacillus*, and most preferably *Lactobacillus rhamnosus*, or other closely microbial related species used in the dairy industry. In a related aspect, methods for producing a microbe having an altered genotype and/or phenotype is provided, such methods comprising transforming a microbial cell with a genetic construct of the present invention to provide a transgenic cell, and cultivating the transgenic cell under conditions conducive to growth and multiplication. Organisms having an altered genotype or phenotype as a result of modulation of the level or content of a polynucleotide or polypeptide of the present invention compared to a wild-type organism, as well as components and progeny of such organisms, are contemplated by and encompassed within the present invention.

The isolated polynucleotides of the present invention may be usefully employed for the detection of lactic acid bacteria, preferably *L. rhamnosus*, in a sample material, using techniques well known in the art, such as polymerase chain reaction (PCR) and DNA hybridization, as detailed below.

The inventive polynucleotides and polypeptides may also be employed in methods for the selection and production of more effective probiotic bacteria; as "bioactive" (health-promoting) ingredients and health supplements, for immune function enhancement; for reduction of blood lipids such as cholesterol; for production of bioactive material from genetically modified bacteria; as adjuvants; for wound healing; in vaccine development, particularly mucosal vaccines; as animal probiotics for improved animal health and productivity; in selection and production of genetically modified rumen microorganisms for improved animal nutrition and productivity, better flavor and improved milk composition; in

methods for the selection and production of better natural food bacteria for improved flavor, faster flavor development, better fermentation characteristics, vitamin synthesis and improved textural characteristics; for the production of improved food bacteria through genetic modification; and for the identification of novel enzymes for the production of, for example, flavors or aroma concentrates.

The isolated polynucleotides of the present invention also have utility in genome mapping, in physical mapping, and in positional cloning of genes of more or less related microbes. Additionally, the polynucleotide sequences identified as SEQ ID NOS: 1-59, and their variants, may be used to design oligonucleotide probes and primers. Oligonucleotide probes and primers have sequences that are substantially complementary to the polynucleotide of interest over a certain portion of the polynucleotide. Oligonucleotide probes designed using the polynucleotides of the present invention may be used to detect the presence and examine the expression patterns of genes in any organism having sufficiently similar DNA and RNA sequences in their cells, using techniques that are well known in the art, such as slot blot DNA hybridization techniques. Oligonucleotide primers designed using the polynucleotides of the present invention may be used for PCR amplifications. Oligonucleotide probes and primers designed using the polynucleotides of the present invention may also be used in connection with various microarray technologies, including the microarray technology of Affymetrix. (Santa Clara, CA).

The polynucleotides of the present invention may also incorporate regulatory elements such as promoters, gene regulators, origins of DNA replication, secretion signals, cell wall or membrane anchors for genetic tools (such as expression or integration vectors).

The polynucleotide sequences, encoded polypeptides and genetic constructs of this invention are useful for improving the properties of microbes that are used in the manufacture of milk-derived products, such as cheeses, yogurt, fermented milk products, sour milks, and buttermilk. Microbial metabolism during fermentation, which results in the breakdown of proteins, lipids and lactose in milk, influences the speed of ripening, the texture and consistency of fermented milk products, and the development of flavors and aromas during ripening. Undesirable flavors in milk products are produced, for example, by the food of milk-producing animals, microbial action, and enzymatic activity during fermentation, and require removal. The present invention provides polynucleotides and polypeptides and methods for their use in modifying the flavor, aroma, texture and health-related benefits of milk-derived products. Methods are described for modulating the polynucleotide content or

composition of microbes used in the dairy industry by transforming the microbes with one or more polynucleotides sequences of *Lactobacillus rhamnosus* strain HN001. The inventive polynucleotides also include sequences encoding polypeptides that increase the survivability of microbes during industrial fermentation processes, wherein exposure to osmotic, temperature and other stresses can lead to reduced microbial viability, impaired metabolic activity and suboptimal fermentation conditions. While the present invention is described with particular reference to milk-derived products, it will be recognized that microbes such as Lactobacillus, which are used in the dairy industry, are also used in the production of other foods and beverages (e.g., fermented vegetables, beer, wines, juices, sourdough breads). It is expected that the polynucleotides described herein and their methods of use can be used for the processing of these foods and beverages as well.

This invention also provides transgenic microbial populations comprising expressible polynucleotide sequences of *Lactobacillus rhamnosus* strain HN001 which health-related benefits. For example, the polypeptides encoded by the inventive sequences include enzymes that detoxify carcinogens, degrade allergenic proteins and lactose, and produce bioactive peptides and biogenic amines. Microbes transformed with these polynucleotide sequences can be taken internally as a probiotic composition or alternatively, the microbes or their encoded polypeptides can be added to products to provide health-related benefits. Nonpathogenic bacteria, preferably lactic-acid producing species of *Bacillus, Lactobacillus, Sporolactobacillus* or *Bifidobacterium*, that are able to colonize the gastrointestinal tract, preferably the gastrointestinal tract of a mammal, are useful for preventing or reducing pathogen colonization of the gastrointestinal mucosa, and for replacing normal flora that are depleted, for example, by drug therapy. The polynucleotide sequences of this invention can be used to transform microbes for use in a therapeutic composition that is effective for treating or preventing a gastrointestinal condition or disorder caused by the presence of pathogenic microbes in the gastrointestinal tract or by the absence of normal intestinal microbes in the intestinal tract. Such probiotic compositions can be administered alone or in combination with another pharmaceutical agent, depending on the condition that is to be treated.

All references cited herein, including patent references and non-patent publications, are hereby incorporated by reference in their entireties.

Brief Description of the Drawings

Fig. 1 shows the nucleotide sequence containing *L. rhamnosus* strain HN001 fibronectin binding protein AB2 showing ATG initiation and translation stop codons (boxed).

Fig. 2 shows the amino acid sequence of HN001 fibronectin binding protein AB2, with the subcloned fibronectin binding domain boxed.

Fig. 3 demonstrates specific blocking of fibronectin binding to HN001 cells by the fibronectin binding protein domain of AB2.

Detailed Description

The polynucleotides disclosed herein were isolated by high throughput sequencing of DNA libraries from the lactic acid bacteria *Lactobacillus rhamnosus* as described in Example 1. Cell wall, cell surface and secreted components of lactic acid bacteria are known to mediate immune modulation, cell adhesion and antibacterial activities, resulting in many beneficial effects including: resistance to enteric pathogens: modulation of cancer, including colon cancer: anti-mutagenesis effects; reduction of small bowel bacterial overgrowth; modulation of auto-immune disorders; reduction in allergic disorders; modulation of urogenital infections, inflammatory bowel disorder, irritable bowel syndrome, *Helicobacter pylori* infection and hepatic encephalopathy; reduction of infection with pathogens; regulation of colonocyte proliferation and differentiation; reduction of mucosal permeability; and relief of constipation and diarrhea. These cell components include, but are not limited to, peptidoglycans, teichoic acids, lipoteichoic acids, polysaccharides, adhesion proteins, secreted proteins, surface layer or S-layer proteins, collagen binding proteins and other cell surface proteins, and antibacterial substances such as bacteriocins and organic acids produced by these bacteria. Polynucleotides involved in the synthesis of these proteins and in the synthesis, modification, regulation, transport, synthesis and/or accumulation of precursor molecules for these proteins can be used to modulate the immune effects, antibacterial, cell adhesion and competitive exclusion effects of the bacteria or of components that might be produced by these bacteria.

In order to function effectively as probiotic bacteria, *L. rhamnosus* HN001 must survive environmental stress conditions in the gastrointestinal tract, as well as commercial and industrial processes. Modification of particular polynucleotides or regulatory processes have been shown to be effective against a number of stresses including oxidative stress, pH, osmotic stress, dehydration, carbon starvation, phosphate starvation, nitrogen starvation, amino acid starvation, heat or cold shock and mutagenic stress. Polynucleotides involved in

stress resistance often confer multistress resistance, i.e., when exposed to one stress, surviving cells are resistant to several non-related stresses. Bacterial genes and/or processes shown to be involved in multistress resistance include:

Intracellular phosphate pools - inorganic phosphate starvation leads to the induction of *pho* regulon genes, and is linked to the bacterial stringent response. Gene knockouts involving phosphate receptor genes appear to lead to multistress resistance.

Intracellular guanosine pools - purine biosynthesis and scavenger pathways involve the production of phosphate-guanosine compounds that act as signal molecules in the bacterial stringent response. Gene knockouts involving purine scavenger pathway genes appear to confer multistress resistance.

Osmoregulatory molecules - small choline-based molecules, such as glycine-betaine, and sugars, such as trehalose, are protective against osmotic shock and are rapidly imported and/or synthesized in response to increasing osmolarity.

Acid resistance - lactobacilli naturally acidify their environment through the excretion of lactic acid, mainly through the *cit* operon genes responsible for citrate uptake and utilization.

Stress response genes - a number of genes appear to be induced or repressed by heat shock, cold shock, and increasing salt through the action of specific promoters.

The isolated polynucleotides of the present invention, and genetic constructs comprising such polynucleotides, may be employed to produce bacteria having desired phenotypes, including increased resistance to stress and improved fermentation properties.

Many enzymes are known to influence dairy product flavor, functional and textural characteristics as well as general fermentation characteristics such as speed of growth, acid production and survival. These enzymes include those involved in the metabolism of lipids, polysaccharides, amino acids and carbohydrates as well as those involved in the lysis of the bacterial cells.

The isolated polynucleotides and polypeptides of the present invention have demonstrated similarity to polynucleotides and/or polypeptides of known function. The

putative identity and functions of the inventive polynucleotides based on such similarities are shown below in Table 1.

TABLE 1

SEQ ID NO Polynucleotide	SEQ ID NO Polypeptide	Category	Gene function or protein class
1	62		Transmembrane protein that participates in the adhesion of bacteria to gut cells, part of an operon containing the mapA gene encoding a mucin binding protein. This gene may be used to identify or manipulate interactions with gut cells.
2	63		Homolog of a 28 kDa antigen and major cell adherence molecule of *Campylobacter jejuni* and *Campylobacter coli*. Significant similarity to amino acid transport proteins in Gram-negative bacteria. This gene may be used to identify or manipulate both interactions with gut cells and amino acid metabolism.
3	64		Histidinol-phosphate aminotransferase, have tyrosine and phenylalanine aminotransferase activity. It is involved in amino acid metabolism and is useful to identify or manipulate metabolism and influence growth and the production of flavor compounds.
4	65		Tyrosine aminotransferase (EC 2.6.1.5) (L-tyrosine:2-oxoglutarate aminotransferase) transfers nitrogenous groups as part of the aromatic amino acid pathway. It is involved in synthesis of flavor compounds and amino acid metabolism. It is used to identify or manipulate metabolism and influence growth and the production of flavor compounds.
5	66		Cysteine desulfurase, a class-V aminotransferase that supplies inorganic sulfide for Fe-S clusters is involved in cysteine metabolism and generation of flavor compounds. It is used to identify or manipulate metabolism and influence growth and the production of flavor compounds.
6	67		Lipase that plays a role in breakdown of triglycerides. It is used to identify or manipulate metabolism and influence growth and the production of flavor compounds.
7	68		O-acetylserine sulfhydrylase is involved in cysteine synthesis. It converts O-acetyl-L-serine and H2S to L-cysteine and acetate. It is involved in synthesis of flavor and aroma compounds and used to identify or manipulate metabolism and influence growth and the production of flavor compounds.
8	69		Surface protein involved in a number of functions including as a collagen and/or mucin binding protein in cellular adhesion and as a cysteine transporter, part of the

SEQ ID NO Polynucleotide	SEQ ID NO Polypeptide	Category	Gene function or protein class
			ABC superfamily, which affects amino acid metabolism and flavor compound synthesis. It is used to identify or manipulate metabolism, growth, the production of flavor compounds, and interactions with gut cells.
9	70		Homolog of Group B streptococcal oligopeptidase, that degrades a variety of bioactive peptides. It is involved in protein breakdown and metabolism, and may impact on flavor compounds as well impact on health through the stability or production of bioactive peptides.
10	71		Homolog of Pz-peptidase, a metalloproteinase and part of the thimet oligopeptidase family. It hydrolyzes the Pz-peptide, 4-phenylazobenzyloxycarbonyl-Pro-Leu-Gly-Pro-Arg. It impacts on flavor compounds as well impact on health through the stability or production of bioactive peptides.
11	72		Adenosine triphosphatase clpC. ATP-dependent Clp proteinase regulatory protein, a pleiotropic regulator controlling growth at high temperatures that is involved in stress response. It is used to identify or impact on the survival or virulence of organisms.
12	73		Homolog of Streptococcal C5a peptidase that specifically cleaves human serum chemotaxin C5a near its C-terminus, destroying its ability to serve as a chemoattractant. It mediates interactions with host immune system and is used to identify or impact on interactions with immune systems.
13	74		Homolog of dipeptidase from *Lactococcus lactis* that hydrolyzes a broad range of dipeptides but no tri, tetra, or larger oligopeptides. It is used to identify or impact on protein metabolism and flavor compound synthesis.
14	75		Acylamino-acid-releasing enzyme (acyl-peptidehydrolase or acylaminoacyl-peptidase) EC 3.4.19.1 that catalyzes removal of N alpha-acetylated amino acid residues from N alpha-acetylated peptides. It is used to identify or impact on metabolism or flavor or aroma compound production.
15	76		Heat shock protease regulatory subunit, the ATPase subunit of an intracellular ATP-dependent protease. It is used to identify or impact on survival or virulence.
16	77		Homologue of O-sialoglycoprotein endopeptidase (EC 3.4.24.57) that hydrolyses O-sialoglycoproteins, but does not cleave unglycosylated proteins, desialylated glycoproteins or N-glycosylated glycoproteins. Sialogylcoproteins can act as receptors for adhesion to gut cells. It is used to identify or impact on interactions with gut cells, protein metabolism, stability or production of bioactive peptides.
17	78		Carboxylesterase that converts a carboxylic ester to an

SEQ ID NO Polynucleotide	SEQ ID NO Polypeptide	Category	Gene function or protein class
			alcohol and a carboxylic acid anion. Esters and alcohols can be potent flavor and aroma compounds. It is used to identify or impact on metabolism or flavor or aroma compound production.
18	79		Glycerophosphodiester phosphodiesterase converts glycerophosphodiesters to an alcohol and glycerol 3-phosphate. Alcohols are potentially important flavor compounds. It is used to identify or impact on metabolism or flavor or aroma compound production.
19	80		Bifunctional alcohol dehydrogenase and acetaldehyde dehydrogenase that plays a role in fermentation of glucose to ethanol under anaerobic conditions. It is used to identify or impact on metabolism or flavor or aroma compound production.
20	81		Short-chain alcohol dehydrogenase is used to identify or impact on metabolism or flavor or aroma compound production.
21	82		Branched chain amino acid transport system II carrier protein that is involved in amino acid metabolism. Amino acid metabolism is important in flavor compound production. It is used to identify or impact on metabolism or flavor compound production.
22	83		Homolog of a human bile salt export pump. Bile tolerance is an important property of probiotic bacteria. Bile salt removal can reduce cholesterol. It can be used to identify or impact on bile tolerance or cholesterol reduction.
23	84		Bifunctional HPr Kinase/P-Ser-HPr phosphatase from *Lactobacillus casei* controls catabolite repression and is involved in phosphate regulation. Phosphate regulation is important in cell survival and stress tolerance. It is used to identify or impact on gene regulation and on stress tolerance.
24	85		Honolog of Suppressor of dominant negative ftsH mutations affecting extracellular protein transport in *E. coli*. It is used to identify or impact on protein transport.
25	86		Malolactic enzyme that converts between malate and lactate. It is central to carbohydrate metabolism, and is also involved in acid tolerance. It is used to identify or impact on metabolism or flavor compound production or cell survival.
26	87		Magnesium transporter, that also has affinity for cobalt. Metal ion transport is necessary for bacterial survival as well as other aspects of metabolism. It is used to identify or impact on metabolism or cell survival.
27	88		Pyruvate dehydrogenase E1 (lipoamide) alpha subunit (EC 1.2.4.1). This glycolytic enzyme is also involved in branched-chain amino acid synthesis and is used to

SEQ ID NO Polynucleotide	SEQ ID NO Polypeptide	Category	Gene function or protein class
			identify or impact on metabolism or flavor or aroma compound production.
28	89		Adhesin is involved in diffuse adherence of diarrhoeagenic *E. coli*. May be used to identify or impact on interactions with gut cells, survival and persistence in the gut.
29	90		dTDP-4-keto-*L. rhamnose* reductase is involved in polysaccharide biosynthesis. Polysaccharides are important for adhesion to gut cells, immune system modulation, stress tolerance and for physical properties of fermented products. It is used to identify or impact on polysaccharide production and interaction with gut cells.
30	91		Glucose inhibited division protein that is involved in stress resistance: gidA mutants are UV-sensitive and exhibit decreased homologous recombination in plasmidic tests. It is used to identify or impact on cell survival and gene regulation.
31	92		Glucose-1-phosphate thymidylyl transferase is involved in polysaccharide biosynthesis. Polysaccharides are important for adhesion to gut cells, immune system modulation, stress tolerance and for physical properties of fermented products. It is used to identify or impact on polysaccharide production and interaction with gut cells.
32	93		Phosphate starvation-induced protein is important for survival under low phospate conditions. Phosphate levels have been shown to be important in multistress resistance. It is used to identify or impact on cell survival.
33	94		Formate C-acetyltransferase (or pyruvate formate lyase, EC 2.3.1.54) converts formate to pyruvate during malate utilization. Pyruvate is central to cell metabolism and is used to identify or impact on metabolism and the generation of flavor compounds.
34	95		Alpha-glycerophosphate oxidase oxidizes alpha-glycerophosphate to dihydroxyacetone phosphate while reducing oxygen to hydrogen peroxide. These compounds are important for metabolism as well as for antimicrobial activity. It is used to identify or impact on metabolism and the generation of flavor compounds as well as antimicrobial activity.
35	96		6-Phosphogluconate dehydrogenase converts 6-phospho-D-gluconate to D-ribulose 5-phosphate and CO2, part of the hexose monophosphate shunt pathway used for carbohydrate metabolism. It is used to identify or impact on metabolism and the generation of flavor compounds.
36	97		5-methyltetrahydropteroyltriglutamate homocysteine methyltransferase converts 5-methyltetrahydropteroyltri-L-glutamate and L-homocysteine toTetrahydropteroyltri-L-glutamate and L-methionine. Sulpher compounds are

SEQ ID NO Polynucleotide	SEQ ID NO Polypeptide	Category	Gene function or protein class
			important in flavor development. Homocysteine is important in cardiovascular health. It is used to identify or impact on metabolism and the generation of flavor or aroma compounds as well as cardiovascular health.
37	98		S-methylmethionine permease is an integral membrane protein involved in S-methylmethionine uptake. Sulfur compounds are important in flavor development, and S-methylmethionine may also be involved in cellular methylation pathways. Cellular methylation is important for gene regulation. It is used to identify or impact on metabolism and the generation of flavor compounds and for cellular methylation.
38	99		6-Phospho-beta-galactosidase is central to lactose metabolism and results in alcohol compounds that may have flavor properties. It is used to identify or impact on metabolism and the generation of flavor compounds.
39	100		GTP binding protein (membrane bound) is involved in the stress response. It is used to identify or impact on cell survival.
40	101		Gamma-glutamyl phosphate reductase (glutamate-5-semialdehyde dehydrogenase) is involved in proline biosynthesis and amino acid metabolism pathways. It is used to identify or impact on metabolism and the generation of flavor compounds.
41	102		Dihydrofolate reductase (EC 1.5.1.3) is responsible for resistance to the cytotoxic drug methotrexate and involved in vitamin synthesis. It is used to identify or impact on metabolism and the generation of vitamin compounds and for drug resistance.
42	103		Lactate dehydrogenase converts lactate to pyruvate, and also has a role in acid tolerance. Lactate can have antimicrobial effects. It is used to identify or impact on metabolism and the generation of flavor compounds, for cell survival and virulence and antimicrobial effects.
43	104		Heat-inducible transcription repressor protein is involved in stress resistance. It is used to identify or impact on survival and on gene regulation.
44	105		Daunorubicin resistance protein (DrrC) is a daunorubicin resistance protein with a strong sequence similarity to the UvrA protein that is involved in excision repair of DNA. DrrC is induced by the anticancer drug daunorubicin and behaves like an ATP-dependent, DNA binding protein in vitro.
45	106		Dihydrodipicolinate synthase (EC 4.2.1.52) (DHDPS) is also known as DapA or AF0910. DapA catalyzes the first step in the biosynthesis of diaminopimelate and lysine from aspartate semialdehyde. The known pathways for

SEQ ID NO Polynucleotide	SEQ ID NO Polypeptide	Category	Gene function or protein class
			diaminopimelate (DAP) and lysine biosynthesis share two key enzymes, dihydrodipicolinate synthase and dihydrodipicolinate reductase, encoded by the dapA and dapB genes, respectively. Diaminopimelate (DAP) is a metabolite that is also involved in peptidoglycan formation. DapA can be used for the industrial production of L-lysine. DHDPS belongs to the DHDPS family.
46	107		Lysin (Lys) is one of the lytic enzymes encoded by bacteriophages. Together with holin, lysis of bacteria used in cheese-making can be achieved to accelerate cheese ripening and to facilitated release of intracellular enzymes for development of flavor formation. Production of holin alone leads to partial lysis of the host cells, whereas production of lysin alone does not cause significant lysis. Model cheese experiments in which an inducible holing/lysin overproducing strain was used showed a fourfold increase in release of L-Lactate dehydrogenase activity into the curd relative to the control strain and the holin-overproducing strain (de Ruyter *et al.*, *Nature Biotechnol.* 15:976-979, 1997), demonstrating the suitability of the system for cheese applications.
47	108		Penicillin-binding protein 1A or PDPF is penicillin-binding protein PBP 1A that is an essential murein polymerases of bacteria. The penicillin binding proteins (PBPs) synthesize and remodel peptidoglycan, the structural component of the bacterial cell wall. Resistance to beta-lactam antibiotics in bacteria is due to alteration of the penicillin-binding proteins (PBPs). PBP 1A belongs to the class A high-molecular-mass PBPs, which harbor transpeptidase (TP) and glycosyltransferase (GT) activities. The GT active site represents a target for the generation of novel non-penicillin antibiotics.
48	109		Virulence-associated protein BH6253 plays a role in the virulence of the pathogens.
49	110		Adherence and virulence protein A (Pav A) is a virulence factor that is widely distributed in bacteria and participates in adherence to host cells and soft tissue pathology.
50	111		Proline iminopeptidase gene (pepI) is part of an operon-like structure of three open reading frames (ORF1, ORF2 and ORF3). ORF1 is preceded by a typical prokaryotic promoter region, and a putative transcription terminator can be found downstream of ORF3, identified as the pepI gene. PepI was shown to be a metal-independent serine peptidase having thiol groups at or near the active site. Kinetic studies identified proline-p-nitroanilide as substrate. PepI is a dimer of M(r) 53,000 (Varmanen *et al.*, *Microbiol.* 142 (Pt 12):3459-68, 1996). The enzyme can

SEQ ID NO Polynucleotide	SEQ ID NO Polypeptide	Category	Gene function or protein class
			be utilized to facilitate the accumulation of proline from dipeptides and oligopeptides during the ripening of cheese.
51	112		Sensory transduction protein regX3 forms part of a two-component regulatory system regX3/senX3 phosphorylated by senX3. The N-terminal region is similar to that of other regulatory components of sensory transduction systems. The senX3-regX3 IR contains a novel type of repetitive sequence, called mycobacterial interspersed repetitive units (MIRUs). The regX3 gene has utility in diagnostic assays to differentiate between bacterial strains.
52	113		Aminopeptidase pepS (EC 3.4.11.-) is part of the proteolytic system of lactic acid bacteria that is essential for bacterial growth in milk and for development of the organoleptic properties of dairy products. PepS is a monomeric metallopeptidase of approximately 45 kDa with optimal activity in the range pH 7.5-8.5 and at 55 degrees C on Arg-paranitroanilide as substrate (Fernandez-Espla and Rul, *Eur. J. Biochem.* 263:502-510, 1999). PepS exhibits a high specificity towards peptides possessing arginine or aromatic amino acids at the N-terminus. PepS is part of the aminopeptidase T family. In view of its substrate specificity, PepS is involved both in bacterial growth by supplying amino acids, and in the development of dairy products' flavor, by hydrolyzing bitter peptides and liberating aromatic amino acids which are important precursors of aroma compounds.
53	114		Phosphoribosylaminoimidazolecarboxamide formyltransferase/imp cyclohydrolase (ec 2.1.2.3) (purH) or AICARFT is biosynthetic enzyme in the *de novo* purine biosynthesis pathway.
54	115		Prolinase (pepR) is a peptidase gene expressing L-proline-beta-naphthylamide-hydrolyzing activity. PepR was shown to be the primary enzyme capable of hydrolyzing Pro-Leu in Lactobacilli. The purified enzyme hydrolyzed Pro-Met, Thr-Leu, and Ser-Phe as well as dipeptides containing neutral, nonpolar amino acid residues at the amino terminus. The isoelectric point of the enzyme was determined to be 4.5 (Shao *et al., Appl. Environ. Microbiol.* 63:3438-3443, 1997). PepR is a serine-dependent protease that can be utilized in production of dairy products where it is used to acidify milk.
55	116		Hexulose-6-phosphate isomerase is also known as HumpI or SGBU and is part of a sugar metabolic pathway along with SGBH where it is involved in isomerization of D-arabino-6-hexulose 3-phosphate to D-fructose 6-phosphate. SGBU belongs to the HumpI family.

SEQ ID NO Polynucleotide	SEQ ID NO Polypeptide	Category	Gene function or protein class
56	117		Succinyl-diaminopimelate desuccinylase encodes the DapE that has utility as antibiotic target.
57	118		Transcriptional regulator (GntR family) is part of the GntR family of DNA binding proteins that has a characteristic helix-turn-helix motif. The motif interacts with DNA double helix and recognizes specific base sequences.
58	119		Xaa-Pro dipeptidase (ec 3.4.13.9) is also known as X-Pro dipeptidase, proline dipeptidase, prolidase, imidodipeptidase or pepQ. PepQ is involved in the hydrolysis of Xaa-|-Pro dipeptides and also acts on aminoacyl-hydroxyproline analogs. PepQ belongs to peptidase family M24b. PepQ can be utilized in the production of cheese.
59	120		Fibronectin binding proteins are expressed by a number of bacteria and been shown to be essential for bacterial adhesion to human epithelial cell surfaces (Holmes *et al.*, *Mol. Microbiol.* 41:1395-1408, 2001; Peacock *et al.*, *Microbiol.* 145:3477-3486, 1999), and may also bind fibrinogen (Kushiro *et al.*, *J. Mol. Microbiol. Biotechnol.* 3:563-571, 2001). Fibronectin binding protein AB2 can be used to alter flavor and aroma in dairy products, to develop products to enhance adhesion to intestinal surface and cell lines, and to enhance survival in intestinal environment. The molecule is also useful to alter metabolic and adhesion characteristics and enhance probiotic effects. It can interact in the human immune system and block or modify adherence of bacteria to mucosal surfaces. Fibronectin can be incorporated as carrier molecules in vaccines.

Isolated polynucleotides of the present invention include the polynucleotides identified herein as SEQ ID NOS: 1-59; isolated polynucleotides comprising a polynucleotide sequence selected from the group consisting of SEQ ID NOS: 1-59; isolated polynucleotides comprising at least a specified number of contiguous residues (*x*-mers) of any of the polynucleotides identified as SEQ ID NOS: 1-59; isolated polynucleotides comprising a polynucleotide sequence that is complementary to any of the above polynucleotides; isolated polynucleotides comprising a polynucleotide sequence that is a reverse sequence or a reverse complement of any of the above polynucleotides; antisense sequences corresponding to any of the above polynucleotides; and variants of any of the above polynucleotides, as that term is described in this specification.

The word "polynucleotide(s)," as used herein, means a single or double stranded polymer of deoxyribonucleotide or ribonucleotide bases and includes DNA and corresponding RNA molecules, including mRNA molecules, both sense and antisense strands of DNA and RNA molecules, and comprehends cDNA, genomic DNA and recombinant DNA, as well as wholly or partially synthesized polynucleotides. A polynucleotide of the present invention may be an entire gene, or any portion thereof. A gene is a DNA sequence which codes for a functional protein or RNA molecule. Operable antisense polynucleotides may comprise a fragment of the corresponding polynucleotide, and the definition of "polynucleotide" therefore includes all operable antisense fragments. Antisense polynucleotides and techniques involving antisense polynucleotides are well known in the art and are described, for example, in Robinson-Benion, *et al.*, "Antisense techniques," *Methods in Enzymol.* 254(23): 363-375, 1995; and Kawasaki, *et al.*, *Artific. Organs* 20 (8): 836-848, 1996.

The definitions of the terms "complement," "reverse complement," and "reverse sequence," as used herein, are best illustrated by the following examples. For the sequence 5' AGGACC 3', the complement, reverse complement, and reverse sequences are as follows:

complement	3' TCCTGG 5'
reverse complement	3' GGTCCT 5'
reverse sequence	5' CCAGGA 3'

Identification of genomic DNA and heterologous species DNA can be accomplished by standard DNA/DNA hybridization techniques, under appropriately stringent conditions, using all or part of a DNA sequence as a probe to screen an appropriate library. Alternatively, PCR techniques using oligonucleotide primers that are designed based on known DNA and protein sequences can be used to amplify and identify other identical or similar DNA sequences. Synthetic DNA corresponding to the identified sequences or variants thereof may be produced by conventional synthesis methods. All of the polynucleotides described herein are isolated and purified, as those terms are commonly used in the art.

The polynucleotides identified as SEQ ID NOS: 1-59 may contain open reading frames ("ORFs"), or partial open reading frames, encoding polypeptides. Additionally, polynucleotides identified as SEQ ID NOS: 1-59 may contain non-coding sequences such as promoters and terminators that may be useful as control elements. Additionally, open reading frames encoding polypeptides may be identified in extended or full-length sequences

corresponding to the sequences set out as SEQ ID NOS: 62-120. Open reading frames may be identified using techniques that are well known in the art. These techniques include, for example, analysis for the location of known start and stop codons, most likely reading frame identification based on codon frequencies, similarity to known bacterial expressed genes, etc. Suitable tools and software for ORF analysis are available, for example, on the Internet at the NCBI's site. Additional tools and software suitable for ORF analysis, include GeneWise (The Sanger Center, Wellcome Trust Genome Campus, Hinxton, Cambridge CB10 1SA, United Kingdom), Diogenes (Computational Biology Centers, University of Minnesota, Academic Health Center, UMHG Box 43 Minneapolis MN 55455), and GRAIL (Informatics Group, Oak Ridge National Laboratories, Oak Ridge, Tennessee, TN). Open reading frames and portions of open reading frames may be identified in the polynucleotides of the present invention. Once a partial open reading frame is identified, the polynucleotide may be extended in the area of the partial open reading frame using techniques that are well known in the art until the polynucleotide for the full open reading frame is identified. Thus, polynucleotides and open reading frames encoding polypeptides may be identified using the polynucleotides of the present invention.

Once open reading frames are identified in the polynucleotides of the present invention, the open reading frames may be isolated and/or synthesized. Expressible genetic constructs comprising the open reading frames and suitable promoters, initiators, terminators, etc., which are well known in the art, may then be constructed. Such genetic constructs may be introduced into a host cell to express the polypeptide encoded by the open reading frame. Suitable host cells may include various prokaryotic and eukaryotic cells. *In vitro* expression of polypeptides is also possible, as well known in the art.

As used herein, the term "oligonucleotide" refers to a relatively short segment of a polynucleotide sequence, generally comprising between 6 and 60 nucleotides, and comprehends both probes for use in hybridization assays and primers for use in the amplification of DNA by polymerase chain reaction.

As used herein, the term "*x*-mer," with reference to a specific value of "*x*," refers to a polynucleotide comprising at least a specified number ("*x*") of contiguous residues of any of the polynucleotides identified as SEQ ID NOS: 1-59. The value of *x* may be from about 20 to about 600, depending upon the specific sequence.

In another aspect, the present invention provides isolated polypeptides encoded, or partially encoded, by the above polynucleotides, including the polypeptides of SEQ ID NOS:

62-120. As used herein, the term "polypeptide" encompasses amino acid chains of any length, including full-length proteins, wherein the amino acid residues are linked by covalent peptide bonds. The term "polypeptide encoded by a polynucleotide" as used herein, includes polypeptides encoded by a polynucleotide which comprises an isolated polynucleotide sequence or variant provided herein. Polypeptides of the present invention may be naturally purified products, or may be produced partially or wholly using recombinant techniques. Such polypeptides may be glycosylated with bacterial, fungal, mammalian or other eukaryotic carbohydrates or may be non-glycosylated.

Polypeptides of the present invention may be produced recombinantly by inserting a polynucleotide that encodes the polypeptide into an expression vector and expressing the polypeptide in an appropriate host. Any of a variety of expression vectors known to those of ordinary skill in the art may be employed. Expression may be achieved in any appropriate host cell that has been transformed or transfected with an expression vector containing a polypeptide encoding a recombinant polypeptide. Suitable host cells include prokaryotes, yeast and higher eukaryotic cells. Preferably, the host cells employed are *Escherichia coli*, *Lactococcus lactis*, *Lactobacillus*, insect, yeast or a mammalian cell line such as COS or CHO. The polynucleotide(s) expressed in this manner may encode naturally occurring polypeptides, portions of naturally occurring polypeptides, or other variants thereof.

In a related aspect, polypeptides are provided that comprise at least a functional portion of a polypeptide having an amino acid sequence encoded by a polynucleotide of the present invention. As used herein, a "functional portion" of a polypeptide is that portion which contains the active site essential for affecting the function of the polypeptide, for example, the portion of the molecule that is capable of binding one or more reactants. The active site may be made up of separate portions present on one or more polypeptide chains and will generally exhibit high binding affinity.

Functional portions of a polypeptide may be identified by first preparing fragments of the polypeptide by either chemical or enzymatic digestion of the polypeptide, or by mutation analysis of the polynucleotide that encodes the polypeptide and subsequent expression of the resulting mutant polypeptides. The polypeptide fragments or mutant polypeptides are then tested to determine which portions retain biological activity, using, for example, the representative assays provided below.

Portions and other variants of the inventive polypeptides may be generated by synthetic or recombinant means. Synthetic polypeptides having fewer than about 100 amino

acids, and generally fewer than about 50 amino acids, may be generated using techniques that are well known to those of ordinary skill in the art. For example, such polypeptides may be synthesized using any of the commercially available solid-phase techniques, such as the Merrifield solid-phase synthesis method, where amino acids are sequentially added to a growing amino acid chain (*See* Merrifield, *J. Am. Chem. Soc.* 85:2149-2154, 1963). Equipment for automated synthesis of polypeptides is commercially available from suppliers such as Perkin Elmer/Applied Biosystems, Inc. (Foster City, CA), and may be operated according to the manufacturer's instructions. Variants of a native polypeptide may be prepared using standard mutagenesis techniques, such as oligonucleotide-directed site-specific mutagensis (Kunkel, *Proc. Natl. Acad. Sci. USA* 82: 488-492, 1985). Sections of DNA sequences may also be removed using standard techniques to permit preparation of truncated polypeptides.

In general, the polypeptides disclosed herein are prepared in an isolated, substantially pure form. Preferably, the polypeptides are at least about 80% pure; more preferably at least about 90% pure; and most preferably at least about 99% pure.

As used herein, the term "variant" comprehends polynucleotide or polypeptide sequences different from the specifically identified sequences, wherein one or more nucleotides or amino acid residues is deleted, substituted, or added. Variants may be naturally occurring allelic variants, or non-naturally occurring variants. Variant polynucleotide sequences preferably exhibit at least 40%, more preferably at least 60%, more preferably yet at least 75%, and most preferably at least 90% identity to a sequence of the present invention. Variant polypeptide sequences preferably exhibit at least 50%, more preferably at least 75%, more preferably yet at least 90%, and most preferably at least 95% identity to a sequence of the present invention. The percentage identity is determined by aligning the two sequences to be compared as described below, determining the number of identical residues in the aligned portion, dividing that number by the total number of residues in the inventive (queried) sequence, and multiplying the result by 100.

Polynucleotide and polypeptide sequences may be aligned, and the percentage of identical residues in a specified region may be determined against another polynucleotide or polypeptide, using computer algorithms that are publicly available. Two exemplary algorithms for aligning and identifying the similarity of polynucleotide sequences are the BLASTN and FASTA algorithms. Polynucleotides may also be analyzed using the BLASTX algorithm, which compares the six-frame conceptual translation products of a nucleotide

query sequence (both strands) against a protein sequence database. The percentage identity of polypeptide sequences may be examined using the BLASTP algorithm. The BLASTN, BLASTX and BLASTP programs are available on the NCBI anonymous FTP server and are available from the National Center for Biotechnology Information (NCBI), National Library of Medicine, Building 38A, Room 8N805, Bethesda, MD 20894, USA. The BLASTN algorithm Version 2.0.4 [Feb-24-1998], Version 2.0.6 [Sept-16-1998] and Version 2.0.11 [Jan-20-2000], set to the parameters described below, is preferred for use in the determination of polynucleotide variants according to the present invention. The BLASTP algorithm, set to the parameters described below, is preferred for use in the determination of polypeptide variants according to the present invention. The use of the BLAST family of algorithms, including BLASTN, BLASTP and BLASTX, is described at NCBI's website at URL http://www.ncbi.nlm.nih.gov/BLAST/newblast.html and in the publication of Altschul *et al.*, *Nucleic Acids Res.* 25: 3389-3402, 1997.

The computer algorithm FASTA is available on the Internet and from the University of Virginia by contacting David Hudson, Vice Provost for Research, University of Virginia, P.O. Box 9025, Charlottesville, VA 22906-9025, USA. FASTA Version 2.0u4 [February 1996], set to the default parameters described in the documentation and distributed with the algorithm, may be used in the determination of variants according to the present invention. The use of the FASTA algorithm is described in Pearson and Lipman, *Proc. Natl. Acad. Sci. USA* 85:2444-2448, 1988; and Pearson, *Methods in Enzymol.* 183: 63-98, 1990.

The following running parameters are preferred for determination of alignments and similarities using BLASTN that contribute to the E values and percentage identity for polynucleotide sequences: Unix running command: blastall -p blastn -d embldb -e 10 –G0 -E0 -r 1 -v 30 -b 30 -i queryseq –o results; the parameters are: -p Program Name [String]; -d Database [String]; -e Expectation value (E) [Real]; -G Cost to open a gap (zero invokes default behavior) [Integer]; -E Cost to extend a gap (zero invokes default behavior) [Integer]; -r Reward for a nucleotide match (BLASTN only) [Integer]; -v Number of one-line descriptions (V) [Integer]; -b Number of alignments to show (B) [Integer]; -i Query File [File In]; and -o BLAST report Output File [File Out] Optional.

The following running parameters are preferred for determination of alignments and similarities using BLASTP that contribute to the E values and percentage identity of polypeptide sequences: blastall –p blastp –d swissprotdb –e 10 -G 0 -E 0 –v 30 –b 30 –i queryseq –o results; the parameters are: -p Program Name [String]; -d Database [String]; -e

Expectation value (E) [Real]; -G Cost to open a gap (zero invokes default behavior) [Integer]; -E Cost to extend a gap (zero invokes default behavior) [Integer]; -v Number of one-line descriptions (v) [Integer]; -b Number of alignments to show (b) [Integer]; -I Query File [File In]; -o BLAST report Output File [File Out] Optional. The "hits" to one or more database sequences by a queried sequence produced by BLASTN, FASTA, BLASTP or a similar algorithm, align and identify similar portions of sequences. The hits are arranged in order of the degree of similarity and the length of sequence overlap. Hits to a database sequence generally represent an overlap over only a fraction of the sequence length of the queried sequence.

The BLASTN, FASTA, and BLASTP algorithms also produce "Expect" values for alignments. The Expect value (E) indicates the number of hits one can "expect" to see over a certain number of contiguous sequences by chance when searching a database of a certain size. The Expect value is used as a significance threshold for determining whether the hit to a database, such as the preferred EMBL database, indicates true similarity. For example, an E value of 0.1 assigned to a polynucleotide hit is interpreted as meaning that in a database of the size of the EMBL database, one might expect to see 0.1 matches over the aligned portion of the sequence with a similar score simply by chance. By this criterion, the aligned and matched portions of the polynucleotide sequences then have a probability of 90% of being the same. For sequences having an E value of 0.01 or less over aligned and matched portions, the probability of finding a match by chance in the EMBL database is 1% or less using the BLASTN or FASTA algorithm.

According to one embodiment, "variant" polynucleotides and polypeptides, with reference to each of the polynucleotides and polypeptides of the present invention, preferably comprise sequences producing an E value of 0.01 or less when compared to the polynucleotide or polypeptide of the present invention. That is, a variant polynucleotide or polypeptide is any sequence that has at least a 99% probability of being the same as the polynucleotide or polypeptide of the present invention, measured as having an E value of 0.01 or less using the BLASTN, FASTA, or BLASTP algorithms set at parameters described above. According to a preferred embodiment, a variant polynucleotide is a sequence having the same number or fewer nucleic acids than a polynucleotide of the present invention that has at least a 99% probability of being the same as the polynucleotide of the present invention, measured as having an E value of 0.01 or less using the BLASTN or FASTA algorithms set at parameters described above. Similarly, according to a preferred

embodiment, a variant polypeptide is a sequence having the same number or fewer amino acids than a polypeptide of the present invention that has at least a 99% probability of being the same as a polypeptide of the present invention, measured as having an E value of 0.01 or less using the BLASTP algorithm set at the parameters described above.

As noted above, the percentage identity is determined by aligning sequences using one of the BLASTN, FASTA, or BLASTP algorithms, set at the running parameters described above, and identifying the number of identical nucleic or amino acids over the aligned portions; dividing the number of identical nucleic or amino acids by the total number of nucleic or amino acids of the polynucleotide or polypeptide sequence of the present invention; and then multiplying by 100 to determine the percentage identity. For example, a polynucleotide of the present invention having 220 nucleic acids has a hit to a polynucleotide sequence in the EMBL database having 520 nucleic acids over a stretch of 23 nucleotides in the alignment produced by the BLASTN algorithm using the parameters described above. The 23 nucleotide hit includes 21 identical nucleotides, one gap and one different nucleotide. The percentage identity of the polynucleotide of the present invention to the hit in the EMBL library is thus 21/220 times 100, or 9.5%. The polynucleotide sequence in the EMBL database is thus not a variant of a polynucleotide of the present invention.

In addition to having a specified percentage identity to an inventive polynucleotide or polypeptide sequence, variant polynucleotides and polypeptides preferably have additional structure and/or functional features in common with the inventive polynucleotide or polypeptide. Polypeptides having a specified degree of identity to a polypeptide of the present invention share a high degree of similarity in their primary structure and have substantially similar functional properties. In addition to sharing a high degree of similarity in their primary structure to polynucleotides of the present invention, polynucleotides having a specified degree of identity to, or capable of hybridizing to an inventive polynucleotide preferably have at least one of the following features: (i) they contain an open reading frame or partial open reading frame encoding a polypeptide having substantially the same functional properties as the polypeptide encoded by the inventive polynucleotide; or (ii) they contain identifiable domains in common.

Alternatively, variant polynucleotides of the present invention hybridize to the polynucleotide sequences recited in SEQ ID NOS: 1-59, or complements, reverse sequences, or reverse complements of those sequences under stringent conditions. As used herein, "stringent conditions" refers to prewashing in a solution of 6X SSC, 0.2% SDS; hybridizing

at 65°C, 6X SSC, 0.2% SDS overnight; followed by two washes of 30 minutes each in 1X SSC, 0.1% SDS at 65° C and two washes of 30 minutes each in 0.2X SSC, 0.1% SDS at 65°C.

The present invention also encompasses polynucleotides that differ from the disclosed sequences but that, as a consequence of the discrepancy of the genetic code, encode a polypeptide having similar enzymatic activity as a polypeptide encoded by a polynucleotide of the present invention. Thus, polynucleotides comprising sequences that differ from the polynucleotide sequences recited in SEQ ID NOS: 1-59, or complements, reverse sequences, or reverse complements of those sequences as a result of conservative substitutions are encompassed within the present invention. Additionally, polynucleotides comprising sequences that differ from the inventive polynucleotide sequences or complements, reverse complements, or reverse sequences as a result of deletions and/or insertions totaling less than 10% of the total sequence length are also contemplated by and encompassed within the present invention. Similarly, polypeptides comprising sequences that differ from the inventive polypeptide sequences as a result of amino acid substitutions, insertions, and/or deletions totaling less than 10% of the total sequence length are contemplated by and encompassed within the present invention, provided the variant polypeptide has similar activity to the inventive polypeptide.

The polynucleotides of the present invention may be isolated from various libraries, or may be synthesized using techniques that are well known in the art. The polynucleotides may be synthesized, for example, using automated oligonucleotide synthesizers (*e.g.*, Beckman Oligo 1000M DNA Synthesizer) to obtain polynucleotide segments of up to 50 or more nucleic acids. A plurality of such polynucleotide segments may then be ligated using standard DNA manipulation techniques that are well known in the art of molecular biology. One conventional and exemplary polynucleotide synthesis technique involves synthesis of a single stranded polynucleotide segment having, for example, 80 nucleic acids, and hybridizing that segment to a synthesized complementary 85 nucleic acid segment to produce a 5-nucleotide overhang. The next segment may then be synthesized in a similar fashion, with a 5-nucleotide overhang on the opposite strand. The "sticky" ends ensure proper ligation when the two portions are hybridized. In this way, a complete polynucleotide of the present invention may be synthesized entirely *in vitro*.

Certain of the polynucleotides identified as SEQ ID NOS: 1-59 are generally referred to as "partial" sequences, in that they do not represent the full coding portion of a gene

encoding a naturally occurring polypeptide. The partial polynucleotide sequences disclosed herein may be employed to obtain the corresponding full-length genes for various species and organisms by, for example, screening DNA expression libraries using hybridization probes based on the polynucleotides of the present invention, or using PCR amplification with primers based upon the polynucleotides of the present invention. In this way one can, using methods well known in the art, extend a polynucleotide of the present invention upstream and downstream of the corresponding DNA, as well as identify the corresponding mRNA and genomic DNA, including the promoter and enhancer regions, of the complete gene. The present invention thus comprehends isolated polynucleotides comprising a sequence identified in SEQ ID NOS: 1-59, or a variant of one of the specified sequences, that encode a functional polypeptide, including full length genes. Such extended polynucleotides may have a length of from about 50 to about 4,000 nucleic acids or base pairs, and preferably have a length of less than about 4,000 nucleic acids or base pairs, more preferably yet a length of less than about 3,000 nucleic acids or base pairs, more preferably yet a length of less than about 2,000 nucleic acids or base pairs. Under some circumstances, extended polynucleotides of the present invention may have a length of less than about 1,800 nucleic acids or base pairs, preferably less than about 1,600 nucleic acids or base pairs, more preferably less than about 1,400 nucleic acids or base pairs, more preferably yet less than about 1,200 nucleic acids or base pairs, and most preferably less than about 1,000 nucleic acids or base pairs.

Polynucleotides and polypeptides of the present invention comprehend polynucleotides and polypeptides comprising at least a specified number of contiguous residues (x-mers) of any of the polynucleotides and polypeptides identified as SEQ ID NOS: 1-59 and 62-120, or their variants. According to preferred embodiments, the value of x is preferably at least 20, more preferably at least 40, more preferably yet at least 60, and most preferably at least 80. Thus, polynucleotides of the present invention include polynucleotides comprising a 20-mer, a 40-mer, a 60-mer, an 80-mer, a 100-mer, a 120-mer, a 150-mer, a 180-mer, a 220-mer a 250-mer, or a 300-mer, 400-mer, 500-mer or 600-mer of a polynucleotide or polypeptide identified as SEQ ID NOS: 1-59 and 62-120 or a variant thereof.

Oligonucleotide probes and primers complementary to and/or corresponding to SEQ ID NOS: 1-59, and variants of those sequences, are also comprehended by the present invention. Such oligonucleotide probes and primers are substantially complementary to the

polynucleotide of interest. An oligonucleotide probe or primer is described as "corresponding to" a polynucleotide of the present invention, including one of the sequences set out as SEQ ID NOS: 1-59 or a variant, if the oligonucleotide probe or primer, or its complement, is contained within one of the sequences set out as SEQ ID NOS: 1-59 or a variant of one of the specified sequences.

Two single stranded sequences are said to be substantially complementary when the nucleotides of one strand, optimally aligned and compared, with the appropriate nucleotide insertions and/or deletions, pair with at least 80%, preferably at least 90% to 95%, and more preferably at least 98% to 100%, of the nucleotides of the other strand. Alternatively, substantial complementarity exists when a first DNA strand will selectively hybridize to a second DNA strand under stringent hybridization conditions. Stringent hybridization conditions for determining complementarity include salt conditions of less than about 1 M, more usually less than about 500 mM and preferably less than about 200 mM. Hybridization temperatures can be as low as 5°C, but are generally greater than about 22°C, more preferably greater than about 30°C and most preferably greater than about 37°C. Longer DNA fragments may require higher hybridization temperatures for specific hybridization. Since the stringency of hybridization may be affected by other factors such as probe composition, presence of organic solvents and extent of base mismatching, the combination of parameters is more important than the absolute measure of any one alone. DNA-DNA hybridization studies may performed using either genomic DNA or DNA derived by preparing cDNA from the RNA present in a sample to be tested.

In addition to DNA-DNA hybridization, DNA-RNA or RNA-RNA hybridization assays are also possible. In the first case, the mRNA from expressed genes would then be detected instead of genomic DNA or cDNA derived from mRNA of the sample. In the second case, RNA probes could be used. In addition, artificial analogs of DNA hybridizing specifically to target sequences could also be used.

In specific embodiments, the oligonucleotide probes and/or primers comprise at least about 6 contiguous residues, more preferably at least about 10 contiguous residues, and most preferably at least about 20 contiguous residues complementary to a polynucleotide sequence of the present invention. Probes and primers of the present invention may be from about 8 to 100 base pairs in length or, preferably from about 10 to 50 base pairs in length or, more preferably from about 15 to 40 base pairs in length. The primers and probes may be readily selected using procedures well known in the art, taking into account DNA-DNA

hybridization stringencies, annealing and melting temperatures, potential for formation of loops and other factors, which are well known in the art. Tools and software suitable for designing probes, and especially suitable for designing PCR primers, are available on the Internet, for example, at the Horizon Press site. In addition, a software program suitable for designing probes, and especially for designing PCR primers, is available from Premier Biosoft International, 3786 Corina Way, Palo Alto, CA 94303-4504. Preferred techniques for designing PCR primers are also disclosed in Dieffenbach and Dyksler, *PCR primer: a laboratory manual*, CSHL Press: Cold Spring Harbor, NY, 1995.

A plurality of oligonucleotide probes or primers corresponding to a polynucleotide of the present invention may be provided in a kit form. Such kits generally comprise multiple DNA or oligonucleotide probes, each probe being specific for a polynucleotide sequence. Kits of the present invention may comprise one or more probes or primers corresponding to a polynucleotide of the present invention, including a polynucleotide sequence identified in SEQ ID NOS: 1-59.

In one embodiment useful for high-throughput assays, the oligonucleotide probe kits of the present invention comprise multiple probes in an array format, wherein each probe is immobilized in a predefined, spatially addressable location on the surface of a solid substrate. Array formats which may be usefully employed in the present invention are disclosed, for example, in U.S. Patents No. 5,412,087, 5,545,531, and PCT Publication No. WO 95/00530, the disclosures of which are hereby incorporated by reference.

Oligonucleotide probes for use in the present invention may be constructed synthetically prior to immobilization on an array, using techniques well known in the art (*See*, for example, Gait, ed., *Oligonucleotide synthesis a practical approach*, IRL Press: Oxford, England, 1984). Automated equipment for the synthesis of oligonucleotides is available commercially from such companies as Perkin Elmer/Applied Biosystems Division (Foster City, CA) and may be operated according to the manufacturer's instructions. Alternatively, the probes may be constructed directly on the surface of the array using techniques taught, for example, in PCT Publication No. WO 95/00530.

The solid substrate and the surface thereof preferably form a rigid support and are generally formed from the same material. Examples of materials from which the solid substrate may be constructed include polymers, plastics, resins, membranes, polysaccharides, silica or silica-based materials, carbon, metals and inorganic glasses. Synthetically prepared

probes may be immobilized on the surface of the solid substrate using techniques well known in the art, such as those disclosed in U.S. Patent No. 5,412,087.

In one such technique, compounds having protected functional groups, such as thiols protected with photochemically removable protecting groups, are attached to the surface of the substrate. Selected regions of the surface are then irradiated with a light source, preferably a laser, to provide reactive thiol groups. This irradiation step is generally performed using a mask having apertures at predefined locations using photolithographic techniques well known in the art of semiconductors. The reactive thiol groups are then incubated with the oligonucleotide probe to be immobilized. The precise conditions for incubation, such as temperature, time and pH, depend on the specific probe and can be easily determined by one of skill in the art. The surface of the substrate is washed free of unbound probe and the irradiation step is repeated using a second mask having a different pattern of apertures. The surface is subsequently incubated with a second, different, probe. Each oligonucleotide probe is typically immobilized in a discrete area of less than about 1 mm^2. Preferably each discrete area is less than about 10,000 mm^2, more preferably less than about 100 mm^2. In this manner, a multitude of oligonucleotide probes may be immobilized at predefined locations on the array.

The resulting array may be employed to screen for differences in organisms or samples or products containing genetic material as follows. Genomic or cDNA libraries are prepared using techniques well known in the art. The resulting target DNA is then labeled with a suitable marker, such as a radiolabel, chromophore, fluorophore or chemiluminescent agent, using protocols well known for those skilled in the art. A solution of the labeled target DNA is contacted with the surface of the array and incubated for a suitable period of time.

The surface of the array is then washed free of unbound target DNA and the probes to which the target DNA hybridized are determined by identifying those regions of the array to which the markers are attached. When the marker is a radiolabel, such as ^{32}P, autoradiography is employed as the detection method. In one embodiment, the marker is a fluorophore, such as fluorescein, and the location of bound target DNA is determined by means of fluorescence spectroscopy. Automated equipment for use in fluorescence scanning of oligonucleotide probe arrays is available from Affymetrix, Inc. (Santa Clara, CA) and may be operated according to the manufacturer's instructions. Such equipment may be employed to determine the intensity of fluorescence at each predefined location on the array, thereby providing a measure of the amount of target DNA bound at each location. Such an assay

would be able to indicate not only the absence and presence of the marker probe in the target, but also the quantitative amount as well.

The significance of such high-throughput screening system is apparent for applications such as microbial selection and quality control operations in which there is a need to identify large numbers of samples or products for unwanted materials, to identify microbes or samples or products containing microbial material for quarantine purposes, etc., or to ascertain the true origin of samples or products containing microbes. Screening for the presence or absence of polynucleotides of the present invention used as identifiers for tagging microbes and microbial products can be valuable for later detecting the genetic composition of food, fermentation and industrial microbes or microbes in human or animal digestive system after consumption of probiotics, etc.

In this manner, oligonucleotide probe kits of the present invention may be employed to examine the presence/absence (or relative amounts in case of mixtures) of polynucleotides in different samples or products containing different materials rapidly and in a cost-effective manner. Examples of microbial species which may be examined using the present invention, include lactic acid bacteria, such as *Lactobacillus rhamnosus*, and other microbial species.

Another aspect of the present invention involves collections of a plurality of polynucleotides and/or polypeptides of the present invention. A collection of a plurality of the polynucleotides and/or polypeptides of the present invention, particularly the polynucleotides and polypeptides identified as SEQ ID NOS: 1-59 and 62-120, may be recorded and/or stored on a storage medium and subsequently accessed for purposes of analysis, comparison, etc. Suitable storage media include magnetic media such as magnetic diskettes, magnetic tapes, CD-ROM storage media, optical storage media, and the like. Suitable storage media and methods for recording and storing information, as well as accessing information such as polynucleotide sequences recorded on such media, are well known in the art. The polynucleotide information stored on the storage medium is preferably computer-readable and may be used for analysis and comparison of the polynucleotide information.

Another aspect of the present invention thus involves storage medium on which are recorded a collection of the polynucleotides and/or polypeptides of the present invention, particularly a collection of the polynucleotides and/or polypeptides identified as SEQ ID NOS: 1-59 and 62-120. According to one embodiment, the storage medium includes a collection of at least 20, preferably at least 50, more preferably at least 100, and most

preferably at least 200 of the polynucleotides of the present invention, preferably the polynucleotides identified as SEQ ID NOS: 1-59, including variants of those polynucleotides.

Another aspect of the present invention involves a combination of polynucleotides, the combination containing at least 5, preferably at least 10, more preferably at least 20, and most preferably at least 50 different polynucleotides and/or polypeptides of the present invention, including polynucleotides and polypeptides selected from SEQ ID NOS: 1-59 and 62-120, and variants of these polynucleotides and polypeptides.

In another aspect, the present invention provides genetic constructs comprising, in the 5'-3' direction, a gene promoter sequence; and an open reading frame coding for at least a functional portion of a polypeptide encoded by a polynucleotide of the present invention. In certain embodiments, the genetic constructs of the present invention also comprise a gene termination sequence. The open reading frame may be oriented in either a sense or antisense direction. Genetic constructs comprising a non-coding region of a gene coding for a polypeptide encoded by the above polynucleotides or a nucleotide sequence complementary to a non-coding region, together with a gene promoter sequence, are also provided. A terminator sequence may form part of this construct. Preferably, the gene promoter and termination sequences are functional in a host organism. More preferably, the gene promoter and termination sequences are common to those of the polynucleotide being introduced. The genetic construct may further include a marker for the identification of transformed cells.

Techniques for operatively linking the components of the genetic constructs are well known in the art and include the use of synthetic linkers containing one or more restriction endonuclease sites as described, for example, by Sambrook *et al.*, in *Molecular cloning: a laboratory manual*, Cold Spring Harbor Laboratories Press: Cold Spring Harbor, NY, 1989. The genetic constructs of the present invention may be linked to a vector having at least one replication system, for example, *E. coli*, whereby after each manipulation, the resulting construct can be cloned and sequenced and the correctness of the manipulation determined.

Transgenic microbial cells comprising the genetic constructs of the present invention are also provided by the present invention, together with microbes comprising such transgenic cells, products and progeny of such microbes, and materials including such microbes. Techniques for stably incorporating genetic constructs into the genome of target microbes, such as *Lactobacillus* species, *Lactococcus lactis* or *E. coli*, are well known in the art of bacterial transformation and are exemplified by the transformation of *E. coli* for sequencing in Example 1.

Transgenic, non-microbial, cells comprising the genetic constructs of the present invention are also provided, together with organisms comprising such transgenic cells, and products and progeny of such organisms. Genetic constructs of the present invention may be stably incorporated into the genomes of non-microbial target organisms, such as fungi, using techniques well known in the art.

In preferred embodiments, the genetic constructs of the present invention are employed to transform microbes used in the production of food products, ingredients, processing aids, additives or supplements and for the production of microbial products for pharmaceutical uses, particularly for modulating immune system function and immunological effects; and in the production of chemoprotectants providing beneficial effects, probiotics and health supplements. The inventive genetic constructs may also be employed to transform bacteria that are used to produce enzymes or substances such as polysaccharides, flavor compounds, and bioactive substances, and to enhance resistance to industrial processes such as drying and to adverse stimuli in the human digestive system. The genes involved in antibiotic production, and phage uptake and resistance in *Lactobacillus rhamnosus* are considered to be especially useful. The target microbe to be used for transformation with one or more polynucleotides or genetic constructs of the present invention is preferably selected from the group consisting of bacterial genera *Lactococcus, Lactobacillus, Streptococcus, Oenococcus, Lactosphaera, Trichococcus, Pediococcus* and others potentially useful in various fermentation industries selected, most preferably, from the group consisting of *Lactobacillus* species in the following list: *Lactobacillus acetotolerans, Lactobacillus acidophilus, Lactobacillus agilis, Lactobacillus alimentarius, Lactobacillus amylolyticus, Lactobacillus amylophilus, Lactobacillus amylovorus, Lactobacillus animalis, Lactobacillus arizonae, Lactobacillus aviarius, Lactobacillus bavaricus, Lactobacillus bifermentans, Lactobacillus brevis, Lactobacillus buchneri, Lactobacillus bulgaricus, Lactobacillus casei, Lactobacillus collinoides, Lactobacillus coryniformis, Lactobacillus crispatus, Lactobacillus curvatus, Lactobacillus delbrueckii, Lactobacillus delbrueckii* subsp. *bulgaricus, Lactobacillus delbrueckii* subsp. *lactis, Lactobacillus farciminis, Lactobacillus fermentum, Lactobacillus fructivorans, Lactobacillus gallinarum, Lactobacillus gasseri, Lactobacillus graminis, Lactobacillus hamsteri, Lactobacillus helveticus, Lactobacillus helveticus* subsp. *jugurti, Lactobacillus hetero, Lactobacillus hilgardii, Lactobacillus homohiochii, Lactobacillus japonicus, Lactobacillus johnsonii, Lactobacillus kefiri, Lactobacillus lactis, Lactobacillus leichmannii, Lactobacillus lindneri, Lactobacillus mali, Lactobacillus*

maltaromicus, Lactobacillus manihotivorans, Lactobacillus mucosae, Lactobacillus murinus, Lactobacillus oris, Lactobacillus panis, Lactobacillus paracasei, Lactobacillus paracasei subsp. *pseudoplantarum, Lactobacillus paraplantarum, Lactobacillus pentosus, Lactobacillus plantarum, Lactobacillus pontis, Lactobacillus reuteri, Lactobacillus rhamnosus, Lactobacillus ruminis, Lactobacillus sake, Lactobacillus salivarius, Lactobacillus salivarius* subsp. *salicinius, Lactobacillus salivarius* subsp. *salivarius, Lactobacillus sanfranciscensis, Lactobacillus sharpeae, Lactobacillus thermophilus, Lactobacillus vaginalis, Lactobacillus vermiforme, Lactobacillus zeae.*

In yet a further aspect, the present invention provides methods for modifying the concentration, composition and/or activity of a polypeptide in a host organism, such as a microbe, comprising stably incorporating a genetic construct of the present invention into the genome of the host organism by transforming the host organism with such a genetic construct. The genetic constructs of the present invention may be used to transform a variety of organisms. Organisms which may be transformed with the inventive constructs include plants, such as monocotyledonous angiosperms (*e.g.*, grasses, corn, grains, oat, wheat and barley); dicotyledonous angiosperms (*e.g.*, *Arabidopsis*, tobacco, legumes, alfalfa, oaks, eucalyptus, maple); gymnosperms, (*e.g.*, Scots pine (Aronen, *Finnish Forest Res. Papers*, Vol. 595, 1996); white spruce (Ellis *et al.*, *Biotechnology* 11:84-89, 1993); and larch (Huang, *et al.*, *In Vitro Cell* 27:201-207, 1991); and any kind of plant amenable to genetic engineering.

Thus, in yet another aspect, transgenic plant cells comprising the genetic constructs of the present invention are provided, together with plants comprising such transgenic cells, and fruits, seeds, products and progeny of such plants. Techniques for stably incorporating genetic constructs into the genome of target organisms, such as plants, are well known in the art and include *Agrobacterium tumefaciens* mediated introduction, electroporation, protoplast fusion, injection into reproductive organs, injection into immature embryos, high velocity projectile introduction and the like. The choice of technique will depend upon the target plant to be transformed. For example, dicotyledonous plants and certain monocots and gymnosperms may be transformed by *Agrobacterium* Ti plasmid technology, as described, for example by Bevan, *Nucleic Acids Res.* 12:8711-8721, 1984. Targets for the introduction of the genetic constructs include tissues, such as leaf tissue, disseminated cells, protoplasts, seeds, embryos, meristematic regions; cotyledons, hypocotyls, and the like.

Once the cells are transformed, cells having the genetic construct incorporated in their genome are selected. Transgenic cells may then be cultured in an appropriate medium, using techniques well known in the art. In the case of protoplasts, the cell wall is allowed to reform under appropriate osmotic conditions. In the case of seeds or embryos, an appropriate germination or callus initiation medium is employed. For explants, an appropriate regeneration medium is used. Regeneration of plants is well established for many species. For a review of regeneration of forest trees, *see* Dunstan *et al.*, "Somatic embryogenesis in woody plants," in Thorpe, T.A., ed., *In vitro embryogenesis of plants, (Current Plant Science and Biotechnology in Agriculture)*, 20(12):471-540, 1995. Specific protocols for the regeneration of spruce are discussed by Roberts et al. ("Somatic embryogenesis of Spruce," *in* Redenbaugh K., ed., *Synseed: applications of synthetic seed to crop improvement*, CRC Press: Ch.23:427-449, 1993). The resulting transformed plants may be reproduced sexually or asexually, using methods well known in the art, to give successive generations of transgenic plants and practically unlimited amounts of tagged plant-derived products.

Polynucleotides of the present invention may also be used to specifically suppress gene expression by methods such as RNA interference (RNAi), which may also include cosuppression and quelling. This and other techniques of gene suppression are well known in the art. A review of this technique is found in *Science* 288:1370-1372, 2000. Traditional methods of gene suppression, employing antisense RNA or DNA, operate by binding to the reverse sequence of a gene of interest such that binding interferes with subsequent cellular processes and thereby blocks synthesis of the corresponding protein. RNAi also operates on a post-transcriptional level and is sequence specific, but suppresses gene expression far more efficiently

Studies have demonstrated that one or more ribonucleases specifically bind to and cleave double-stranded RNA into short fragments. The ribonuclease(s) remains associated with these fragments, which in turn specifically bind to complementary mRNA, i.e. specifically bind to the transcribed mRNA strand for the gene of interest. The mRNA for the gene is also degraded by the ribonuclease(s) into short fragments, thereby obviating translation and expression of the gene. Additionally, an RNA polymerase may act to facilitate the synthesis of numerous copies of the short fragments, which exponentially increases the efficiency of the system. A unique feature of this gene suppression pathway is that silencing is not limited to the cells where it is initiated. The gene-silencing effects may

be disseminated to other parts of an organism and even transmitted through the germ line to several generations.

Specifically, polynucleotides of the present invention are useful for generating gene constructs for silencing specific genes. Polynucleotides of the present invention may be used to generate genetic constructs that encode a single self-complementary RNA sequence specific for one or more genes of interest. Genetic constructs and/or gene-specific self-complementary RNA sequences may be delivered by any conventional method known in the art. Within genetic constructs, sense and antisense sequences flank an intron sequence arranged in proper splicing orientation making use of donor and acceptor splicing sites. Alternative methods may employ spacer sequences of various lengths rather than discrete intron sequences to create an operable and efficient construct. During post-transcriptional processing of the gene construct product, intron sequences are spliced-out, allowing sense and antisense sequences, as well as splice junction sequences, to bind forming double-stranded RNA. Select ribonucleases bind to and cleave the double-stranded RNA, thereby initiating the cascade of events leading to degradation of specific mRNA gene sequences, and silencing specific genes. Alternatively, rather than using a gene construct to express the self-complementary RNA sequences, the gene-specific double-stranded RNA segments are delivered to one or more targeted areas to be internalized into the cell cytoplasm to exert a gene silencing effect.

Using this cellular pathway of gene suppression, gene function may be studied and high-throughput screening of sequences may be employed to discover sequences affecting gene expression. Additionally, genetically modified microbes and higher order organisms may be generated.

The following examples are offered by way of illustration and not by way of limitation.

Example 1

Isolation and Characterization of DNA Sequences from *Lactobacillus rhamnosus* strain HN001

Lactobacillus rhamnosus strain HN001 DNA libraries were constructed and screened as follows.

DNA was prepared in large scale by cultivating the bacteria in 2 x 100 ml cultures with 100 ml MRS broth (Difco Laboratories, Detroit MI) and 1 ml *Lactobacillus* glycerol stock as inoculum, placed into 500 ml culture flasks and incubated at 37 °C for approx. 16 hours with shaking (220 rpm).

The cultures were centrifuged at 6200 rpm for 10 min to pellet the cells. The supernatant was removed and the cell pellet resuspended in 40 ml fresh MRS broth and transferred to clean 500 ml culture flasks. Fresh MRS broth (60 ml) was added to bring the volume back to 100 ml and flasks were incubated for a further 2 hrs at 37°C with shaking (220 rpm). The cells were pelleted by centrifugation (6200 rpm for 10 min) and supernatant removed. Cell pellets were washed twice in 20 ml buffer A (50 mM NaCl, 30 mM Tris pH 8.0, 0.5 mM EDTA).

Cells were resuspended in 2.5 ml buffer B (25% sucrose (w/v), 50 mM Tris pH 8.0, 1 mM EDTA, 20 mg/ml lysozyme, 20 μg/ml mutanolysin) and incubated at 37 °C for 45 min. Equal volumes of EDTA (0.25 M) was added to each tube and allowed to incubate at room temperature for 5 min. 20% SDS (1 ml) solution was added, mixed and incubated at 65 °C for 90 min. 50 μl Proteinase K (Gibco BRL, Gaithersburg, MD) from a stock solution of 20 mg/ml was added and tubes incubated at 65 °C for 15 min.

DNA was extracted with equal volumes of phenol:chloroform:isoamylalcohol (25:24:1). Tubes were centrifuged at 6200 rpm for 40 min. The aqueous phase was removed to clean sterile Oak Ridge centrifuge tubes (30 ml). Crude DNA was precipitated with an equal volume of cold isopropanol and incubated at -20 °C overnight.

After resuspension in 500 μl TE buffer, DNase-free RNase was added to a final concentraion of 100 μg/ml and incubated at 37 °C for 30 min. The incubation was extended for a further 30 min after adding 100 μl Proteinase K from a stock solution of 20 mg/ml. DNA was precipitated with ethanol after a phenol:chloroform:isoamylalcohol (25:24:1) and a chloroform:isoamylalcohol (24:1) extraction and dissolved in 250 μl TE buffer.

DNA was digested with *Sau*3AI at a concentration of 0.004 U/μg in a total volume of 1480 μl, with 996 μl DNA, 138.75 μl 10X REACT 4 buffer and 252.75 μl H_2O. Following incubation for 1 hour at 37 °C, DNA was divided into two tubes. 31 μl 0.5 M EDTA was added to stop the digestion and 17 μl samples were taken for agarose gel analysis. Samples were put into 15 ml Falcon tubes and diluted to 3 ml for loading onto sucrose gradient tubes.

Sucrose gradient size fractionation was conducted as follows. 100 ml of 50% sucrose (w/v) was made in TEN buffer (1M NaCl, 20 mM Tris pH 8.0, 5 mM EDTA) and sterile

filtered. Dilutions of 5, 10, 15, 20, 25, 30, 62 and 40% sucrose were prepared and overlaid carefully in Beckman Polyallomer tubes, and kept overnight at 4°C. TEN buffer (4 ml) was loaded onto the gradient, with 3 ml of DNA solution on top. The gradients were centrifuged at 26K for 18 hours at 4°C in a Centricon T-2060 centrifuge using a Kontron TST 28-38 rotor. After deceleration without braking (approx. 1 hour), the gradients were removed and fractions collected using an auto Densi-Flow (Haake-Buchler Instruments). Agarose gel was used to analyse the fractions. The best two pairs of fractions were pooled and diluted to contain less than 10% sucrose. TEN buffer (4 ml) was added and DNA precipitated with 2 volumes of 100% ice cold ethanol and an overnight incubation at -20°C.

DNA pellets were resuspended in 300 µl TE buffer and re-precipitated for approx. 6 hours at -20 °C after adding 1/10 volume 3 M NaOAC pH 5.2 and 2 volumes of ethanol. DNA was pelleted at top speed in a microcentrifuge for 15 min, washed with 70% ethanol and pelleted again, dried and resuspended in 10 µl TE buffer.

DNA was ligated into dephosphorylated *Bam*HI–digested pBluescript SK II$^+$ and dephosphorylated *Bam*HI-digested lambda ZAP Express using standard protocols. Packaging of the DNA was done using Gigapack III Gold packaging extract (Stratagene, La Jolla, CA) following the manufacturer's protocols. Packaged libraries were stored at 4 °C.

Mass excision from the primary packaged phage library was done using XL1-Blue MRF' cells and ExAssist Helper Phage (Stratagene). The excised phagemids were diluted with NZY broth (Gibco BRL, Gaithersburg, MD) and plated out onto LB-kanamycin agar plates containing 5-bromo-4-chloro-3-indolyl-β-D-galactoside (X-gal) and isopropylthio-beta-galactoside (IPTG). After incubation, single colonies were picked for PCR size determination before the most suitable libraries were selected for sequencing.

Of the colonies picked for DNA minipreps and subsequent sequencing, the large majority contained an insert suitable for sequencing. Positive colonies were cultured in LB broth with kanamycin or ampicillin depending on the vector used, and DNA was purified by means of rapid alkaline lysis minipreps (solutions: Qiagen, Venlo, The Netherlands; clearing plates, Millipore, Bedford, MA). Agarose gels at 1% were used to screen sequencing templates for chromosomal contamination and concentration. Dye terminator sequencing reactions were prepared using a Biomek 2000 robot (Beckman Coulter, Inc., Fullerton, CA) and Hydra 96 (Robbins Scientific, Sunnyvale, CA) for liquid handling. DNA amplification was done in a 9700 PCR machine (Perkin Elmer/Applied Biosystems, Foster City, CA) according to the manufacturer's protocol.

The sequence of the genomic DNA fragments were determined using a Perkin Elmer/Applied Biosystems Division Prism 377 sequencer.

To extend the sequences of the inserts from these clones, primers were designed from the determined nucleotide sequences so that the primer sequences are located approximately 100 bp downstream of the 5' end and 100 bp upstream of the 3' end of the determined nucleotide sequence. Selection of primers were done with the Gap4 Genome Assembly Program (Bonfield *et al.*, *Nucleic Acids Res.* 24:4992-4999, 1995 using the following parameters: No. of bases ahead: 40; No. of bases back: 40; Minimum melting temperature: 55°C; maximum melting temperature: 60°C; minimum length: 17 bp; maximum length: 20 bp; minimum GC-content: 40%; maximum GC-content: 60%. Sequencing of clones was done as described above. The determined nucleotide sequences are identified as SEQ ID NOS: 1-59 disclosed herein.

This example not only shows how the sequences were obtained, but also that a bacterium (*E. coli*) can be stably transformed with any desired DNA fragment of the present invention for permanent marking for stable inheritance.

The determined DNA sequences were compared to and aligned with known sequences in the public databases. Specifically, the polynucleotides identified in SEQ ID NO: 1-59 were compared to polynucleotides in the EMBL database as of the end of July 2000, using BLASTN algorithm Version 2.0.11 [Jan-20-2000], set to the following running parameters: Unix running command: blastall -p blastn -d embldb -e 10 -G 0 -E 0 -r 1 -v 30 -b 30 -i queryseq –o results. Multiple alignments of redundant sequences were used to build up reliable consensus sequences. Based on similarity to known sequences, the isolated polynucleotides of the present invention identified as SEQ ID NOS: 1-59 were identified as encoding polypeptides having similarity to the polypeptides shown above in Table 1. The amino acid sequences encoded by the DNA sequences of SEQ ID NO: 1-59 are provided in SEQ ID NO: 62-120, respectively.

Several of the sequences provided in SEQ ID NO: 1-59 were found to be full-length and to contain open reading frames (ORFs). Specifically, SEQ ID NOS: 1; 2; 4-9; 11; 17; 18; 22; 30; 32; 38; 40; 41; 50; 51; 55; 57 and 59 were found to be full-length. The location of ORFs (by nucleotide position) contained within SEQ ID NOS: 1-62, and the corresponding amino acid sequences are provided in Table 2 below.

TABLE 2

Polynucleotide SEQ ID NO:	Open reading frame	Polypeptide SEQ ID NO:
1	1 - 672	62
2	1 – 1,419	63
3	1 – 1,104	64
4	1 - 891	65
5	1 – 1,158	66
6	1 - 786	67
7	1 - 927	68
8	1 - 810	69
9	1 – 1,422	70
10	1 - 768	71
11	1 – 1,923	72
12	1 – 1,443	73
13	1 - 993	74
14	1 – 1,032	75
15	1 – 1,674	76
16	1 - 876	77
17	1 - 732	78
18	1 – 1,299	79
19	1 – 1,344	80
20	1 - 474	81
21	1 – 1,239	82
22	1 – 1,881	83
23	1 - 606	84
24	1 – 1,023	85
25	1 – 1,227	86
26	1 – 1,158	87
27	1 – 1,071	88
28	1 – 1,308	89
29	1 - 645	90
30	1 – 1,920	91
31	1 - 762	92
32	1 - 936	93
33	1 - 840	94
34	1 – 1,341	95
35	1 - 726	96
36	1 - 972	97
37	1 - 888	98
38	1 – 1,422	99
39	1 - 774	100
40	1 – 1,254	101
41	1 - 489	102
42	1 - 285	103
43	1 - 969	104
44	417 – 1,336	105
45	1 - 760	106

Polynucleotide SEQ ID NO:	Open reading frame	Polypeptide SEQ ID NO:
46	193 – 846	107
47	463 – 1,310	108
48	628 – 1,662	109
49	1 - 887	110
50	251 - 946	111
51	66 - 743	112
52	1 - 780	113
53	256 – 1,569	114
54	274 – 1,112	115
55	8 - 954	116
56	17 - 948	117
57	206 – 1,006	118
58	1 – 1,563	119
59	371 - 2048	120

Example 2

Isolation and Characterisation of Fibronectin Binding Protein from *L. rhamnosus* HN001

The full-length polynucleotide sequence of fibronectin binding protein from *L. rhamnosus* strain HN001, given in SEQ ID NO: 59 is shown in Fig. 1 with ATG initiation and translation stop codons (boxed). Based on amino acid sequence similarity between the *Streptococcus pyogenes* fibronectin bind protein FBP54 and the HN001 protein AB2, nucleotides encoding the fibronectin binding domain from AB2 was amplified by PCR and cloned into the pGEX-6P-3 expression vector. The primer sequences used are given in SEQ ID NOS: 60 and 61 and were tagged with *Eco*RI and *Bam*HI restriction endonuclease recognition sequences, respectively, to facilitate cloning. Cloned *AB2* fibronectin binding domain sequence was transformed into *E. coli* DH5α cells according to standard laboratory methods. The polypeptide sequence of fibronectin binding protein AB2 is given in SEQ ID NO: 120 and shown in Fig. 2, showing the fibronectin binding domain (boxed). The AB2 fibronectin binding domain was expressed as a fusion protein with glutathione S-transferase (GST), and purified using Glutathione Sepharose 4B resin (Pharmacia Biotech) according to the manufacturer's instructions. An aliquot of the purified AB2 fibronectin binding domain-GST fusion protein was checked by SDS-PAGE analysis.

To analyze the fibronectin binding activity of the cloned AB2 fragment, a competition assay was performed such that the ability of unlabeled AB2 fibronectin binding domain-GST

fusion protein to block the binding of iodine-125 labeled fibronectin to HN001 was compared to GST and bovine serum albumin (BSA).

A commercial preparation of fibronectin (Sigma) was radio-iodinated 0.1 mCi iodine-125 (Amersham Pharmacia) using IODO-BEADS iodination reagent (Pierce) and separated from unincorporated iodine-125 and excess sodium iodide-125 using a PD-10 desalting column (Amersham-Pharmacia) according to the manufacturer's instructions except that the elution was performed in phosphate buffered saline in twelve 500 µl aliquots. Radioactivity in eluted fractions was quantitated on a Bioscan Quick Count QC-4000/XER Benchtop Radioisotope Counter (Bioscan, Inc.) and fractions containing the first peak of radioactivity (corresponding to labeled fibronectin) were pooled and diluted to 1.5 ng/µl.

A 100 µl aliquot of an overnight culture of HN001 cells was inoculated into 10 ml MRS broth and incubated at 37 °C for 18 hrs, after which a series of 100 µl aliquots were taken for assay. To each aliquot of cells, 30 ng of iodine-125-labeled fibronectin and 30 µg of unlabeled protein in 250 µl phosphate buffered saline pH 7.4 (PBS). After 1 hr incubation at room temperature, 1.5 ml of ice-cold PBS with 0.1% Tween 20 (Sigma) was added, cultures centrifuged to pellet cells and supernatants removed. Radioactive levels in the pellets were measured as above. Results were compared to blank control without HN001 cells to measure background protein binding. Results are the means triplicate samples and presented as the percent radioactivity (dpm) of the bacterial pellet compared to the radioactivity of the added iodine-125-labeled fibronectin ± twice the standard error (Table 1, Figure 3).

Table 3. Proportion of radioactively-labeled fibronectin bound to HN001 cells after co-incubation with unlabeled AB2 fibronectin binding domain-GST-fusion protein, BSA, GST only, and background fibronectin binding (no cell control).

Unlabeled Protein	Mean % Bound Labeled Fibronectin
BSA	4.7 ± 0.3
AB2-GST	2.3 ± 0.3
GST	3.3 ± 0.1
no cells	1.7 ± 0.1

The results in Fig. 3 indicate that while in the presence of 30 µg BSA 4.7% of the total fibronectin added at the start of the assay remained bound to HN001 cells after washing, this level dropped to 2.3% in the presence of unlabeled AB2 fibronectin binding domain-GST

fusion protein. This was significantly lower than fibronectin binding in the presence of GST protein alone and approached the level of background fibronectin binding seen in the absence of HN001 cells. Thus, the HN001 AB2 protein contains a domain capable of specifically blocking fibronectin binding to HN001 cells indicating that the *AB2* gene encodes a fibronectin binding protein.

Fibronectin binding proteins are expressed by a number of bacteria and been shown to be essential for bacterial adhesion to human epithelial cell surfaces (Holmes *et al., Mol. Microbiol.* 41:1395-1408, 2001; Peacock *et al., Microbiology* 145:3477-3486, 1999), and may also bind fibrinogen (Kushiro *et al., J. Mol. Microbiol. Biotechnol.* 3:563-571, 2001). Applications for HN001 fibronectin binding protein AB2 include:

- enhanced adhesion to intestinal surface and cell lines;
- enhanced survival in intestinal environment;
- altered metabolic characteristics;
- altered adhesion characteristics
- altered flavor or aroma characteristics;
- enhanced probiotic effects;
- human immune system interaction
- reagents to block or modify adherence of bacteria to mucosal surfaces; and
- development of vaccine carriers

These attributes may be produced in food, such as dairy, systems (including milk protein hydrolysates and cheese) by directed activity of the enzyme, either in a bacterial strain (including strain HN001, or starter cultures) or as an enzyme preparation.

SEQ ID NOS: 1-120 are set out in the attached Sequence Listing. The codes for nucleotide sequences used in the attached Sequence Listing, including the symbol "n," conform to WIPO Standard ST.25 (1998), Appendix 2, Table 1.

While in the foregoing specification this invention has been described in relation to certain preferred embodiments, and many details have been set forth for purposes of illustration, it will be apparent to those skilled in the art that the invention is susceptible to additional embodiments and that certain of the details described herein may be varied considerably without departing from the basic principles of the invention.

We claim:

1. An isolated polynucleotide comprising a nucleotide sequence present in *Lactobacillus rhamnosus* strain HN001 that encodes a polypeptide having at least one of the following activities: enzyme activity; anti-infection activity; lactose digestion modulating activity; immune system modulating activity; amino acid, lipid, vitamin or carbohydrate metabolic activity; flavor, texture or aroma modulating activity; multistress resistance and survival activity; antigenic activity; adhesion activity; and regulatory activity.

2. An isolated polynucleotide of claim 1, comprising a nucleotide sequence selected from the group consisting of: (1) the sequences recited in SEQ ID NOS: 1-59; and (2) sequences comprising a nucleotide sequence producing an Expectation ("E") value of 0.01 or less when compared to a sequence of (1) above using the BLASTN algorithm version 2.04 set to the default parameters described in the specification, above.

3. An isolated polynucleotide of claim 1 comprising a nucleotide sequence having at least 75% identical nucleotides to a compare sequence selected from the nucleotide sequences recited in SEQ ID NOS: 1-59, the percentage identical nucleotides being determined by aligning the sequence and the compare sequences using the BLASTN algorithm version 2.04 set at default parameters, identifying the number of identical nucleotides over aligned portions of the sequence and the compare sequences, dividing the number of identical nucleotides by the total number of nucleic acids of the compare sequence, and multiplying by 100 to determine the percentage identical nucleotides.

4. An isolated polynucleotide of claim 1 comprising a nucleotide sequence that hybridizes to a polynucleotide comprising a sequence recited in SEQ ID NOS: 1-59 under stringent hybridization conditions;

5. An isolated polynucleotide comprising a nucleotide sequence selected from the group consisting of: (1) complements of the sequences recited in SEQ ID NOS: 1-59; (2) reverse complements of the sequences recited in SEQ ID NOS: 1-59; and (3) reverse sequences of the sequences recited in SEQ ID NOS: 1-59.

6. An isolated polynucleotide comprising a nucleotide sequence selected from the group consisting of: (1) sequences comprising a nucleotide sequence that is a 200-mer of a sequence of claim 2; (2) sequences comprising a nucleotide sequence that is a 100-mer of a sequence of claim 2; and (3) sequences comprising a nucleotide sequence that is a 40-mer of a sequence recited in claim 2.

7. An isolated polynucleotide of claim 1 comprising a nucleotide sequence that differs from a nucleotide sequence recited in SEQ ID NOS: 1-59 as a result of conservative substitutions.

8. An isolated polynucleotide of claim 1 comprising a nucleotide sequence that differs from a nucleotide sequence recited in SEQ ID NOS: 1-59 as a result of deletions and/or insertions and/or substitutions totaling less than 10% of the total sequence length.

9. An isolated polynucleotide of claim 1 comprising a nucleotide sequence that differs from a nucleotide sequence recited in SEQ ID NOS: 1-59 as a result of substitutions, insertions, and/or deletions totaling less than 15% of the total sequence length.

10. An isolated polypeptide encoded by an isolated polynucleotide of any of claims 1-9.

11. An isolated polypeptide comprising an amino acid sequence selected from the group consisting of : (1) the sequences recited in SEQ ID NOS: 62-120; (2) sequences producing an producing an Expectation ("E") value of 0.01 or less when compared to a sequence recited in (1) above using the BLASTP algorithm version 2.0.11 set to default parameters; (3) sequences comprising an amino acid sequence having at least 75% identical amino acid residues with a compare sequence selected from the amino acid sequences recited in (1) and (2) above, the percentage identical amino acids being determined by aligning the sequence and the compare sequences using the BLASTP algorithm version 2.0.11 set at default parameters, identifying the number of identical amino acids over aligned portions of the sequence and the compare sequences, dividing the number of identical amino acids by the total number of amino acids of the compare sequence, and multiplying by 100 to determine the percentage identical amino acids; (4) sequences differing by codon alterations that reflect the

degeneracy of the genetic code; and (5) functionally similar sequences differing only by conservative amino acid substitutions.

12. A fusion protein comprising at least one polypeptide according to claim 11.

13. A kit comprising a plurality of oligonucleotide probes or primers comprising at least 10 contiguous residues complementary to 10 contiguous residues of a nucleotide sequence recited in claim 2.

14. A genetic construct comprising a polynucleotide of claim 2.

15. The genetic construct of claim 14, wherein said polynucleotide encodes a polypeptide that modifies the flavor, aroma, texture and health-related benefits of milk-derived products selected from the group consisting of: histidinol-phosphate aminotransferase, tyrosine aminotransferase, cysteine desulfurase, lipase, O-acetylserine sulfhydrylase, surface protein, Group B streptococcal oligopeptidase, Pz-peptidase, dipeptidase, acylaminoacyl-peptidase, carboxylesterase, glycerophosphodiester phosphodiesterase, bifunctional alcohol dehydrogenase and acetaldehyde dehydrogenase, short-chain alcohol dehydrogenase, branched chain amino acid transport system II carrier protein, malolactic enzyme, pyruvate dehydrogenase, E1 (lipoamide) alpha subunit, formate C-acetyltransferase, 6-phosphogluconate dehydrogenase, 5-methyltetrahydropteroyltriglutamate homocysteine methyltransferase, S-methylmethionine permease, 6-phospho-beta-galactosidase, gamma-glutamyl phosphate reductase, dihydrofolate reductase, lactate dehydrogenase, lysine, aminopeptidase pepS, fibronectin binding protein AB2, prolinase (pepR), Xaa-Pro dipeptidase and human bile salt export pump.

16. The genetic construct of claim 14, wherein said polynucleotide encodes a polypeptide that increases the survivability of a microbe used in the manufacture of dairy products and probiotic supplements, wherein said polypeptide is selected from the group consisting of: transmembrane adhesion protein (SEQ ID NO: 1), major cell adherence molecule of *Campylobacter jejuni* and *Campylobacter coli*, collagen/mucin binding protein (SEQ ID NO: 8), ATP-dependent ClpC proteinase regulatory protein, O-sialoglycoprotein endopeptidase, human bile salt export pump, adhesin (SEQ ID

NO: 28), bifunctional HPr Kinase/P-Ser-HPr phosphatase, malolactic enzyme, magnesium transporter, dTDP-4-keto-*L. rhamnose* reductase, glucose inhibited division protein, glucose-1-phosphate thymidylyl transferase, phosphate starvation-induced protein, GTP binding protein, gamma-glutamyl phosphate reductase, Pav A, aminopeptidase pepS, heat-inducible transcription repressor protein, phosphoribosylaminoimidazolecarboxyamide formyltransferase/imp cyclohydrolase, hexulose-6-phosphate isomerase and fibronectin binding protein AB2.

17. A transgenic cell comprising a genetic construct according to any of claims 14-16.

18. A genetic construct comprising, in the 5'-3' direction:

(a) a gene promoter sequence;

(b) a polynucleotide sequence comprising at least one of the following: (1) a polynucleotide coding for at least a functional portion of a polypeptide encoded by a nucleotide sequence described in claim 2; and (2) a polynucleotide comprising a non-coding region of a gene coding for an polypeptide encoded by a nucleotide sequence selected from the group consisting of sequences recited in claim 2; and

(c) a gene termination sequence.

19. The genetic construct of claim 14-16 or 18 wherein the polynucleotide is in a sense orientation.

20. The genetic construct of claim 14-16 or 18 wherein the polynucleotide is in an antisense orientation.

21. The genetic construct of claim 18, wherein the gene promoter sequence and gene termination sequences are functional in a prokaryote or eucaryote.

22. A method for modulating the polynucleotide content or composition of an organism comprising transforming the organism with a genetic construct of claim 14-16 or 18.

23. A method for improving the properties of microbes used in the manufacture of milk-derived products and probiotic supplements, which comprises modulating the polynucleotide content or composition of said microbes by transforming said microbes with one or more polynucleotide sequences selected from the group consisting of:

(a) *Lactobacillus rhamnosus* strain HN001 sequences encoding polypeptides that modify the flavor, aroma, texture and health-related benefits of milk-derived products; and

(b) *Lactobacillus rhamnosus* strain HN001 sequences encoding polypeptides that increase the survivability of said microbes in dairy product manufacturing processes.

24. The method of claim 23, wherein said polypeptides are selected from the group consisting of: histidinol-phosphate aminotransferase, tyrosine aminotransferase, cysteine desulfurase, lipase, O-acetylserine sulfhydrylase, surface protein, Group B streptococcal oligopeptidase, Pz-peptidase, dipeptidase, acylaminoacyl-peptidase, carboxylesterase, glycerophosphodiester phosphodiesterase, bifunctional alcohol dehydrogenase and acetaldehyde dehydrogenase, short-chain alcohol dehydrogenase, branched chain amino acid transport system II carrier protein, malolactic enzyme, pyruvate dehydrogenase, E1 (lipoamide) alpha subunit, formate C-acetyltransferase, 6-phosphogluconate dehydrogenase, 5-methyltetrahydropteroyltriglutamate homocysteine methyltransferase, S-methylmethionine permease, 6-phospho-beta-galactosidase, gamma-glutamyl phosphate reductase, dihydrofolate reductase, lactate dehydrogenase, lysin, aminopeptidase pepS, fibronectin binding protein AB2, prolinase (pepR), Xaa-Pro dipeptidase, human bile salt export pump, transmembrane adhesion protein (SEQ ID NO: 1), major cell adherence molecule of *Campylobacter jejuni* and *Campylobacter coli*, collagen/mucin binding protein (SEQ ID NO: 8), ATP-dependent ClpC proteinase regulatory protein, O-sialoglycoprotein endopeptidase, adhesin (SEQ ID NO: 28), bifunctional HPr Kinase/P-Ser-HPr phosphatase, malolactic enzyme, magnesium transporter, dTDP-4-keto-*L. rhamnose* reductase, glucose inhibited division protein, glucose-1-phosphate thymidylyl transferase, phosphate starvation-induced protein, GTP binding protein, Pav A, heat-inducible transcription repressor protein, hosphoribosylaminoimidazolecarboxyamide formyltransferase/imp cyclohydrolase, and hexulose-6-phosphate isomerase.

25. A method for modifying the flavor, aroma, texture and/or nutritional and health 'benefits of milk-derived products, which comprises adding one or more polypeptides to the milk being processed, wherein said polypeptides are selected from the group consisting of *Lactobacillus rhamnosus* strain HN001 histidinol-phosphate aminotransferase, tyrosine aminotransferase, cysteine desulfurase, lipase, O-acetylserine sulfhydrylase, surface protein, Group B streptococcal oligopeptidase, Pz-peptidase, dipeptidase, acylaminoacyl-peptidase, carboxylesterase, glycerophosphodiester phosphodiesterase, bifunctional alcohol dehydrogenase and acetaldehyde dehydrogenase, short-chain alcohol dehydrogenase, branched chain amino acid transport system II carrier protein, malolactic enzyme, pyruvate dehydrogenase, E1 (lipoamide) alpha subunit, formate C-acetyltransferase, 6-phosphogluconate dehydrogenase, 5-methyltetrahydropteroyltriglutamate homocysteine methyltransferase, S-methylmethionine permease, 6-phospho-beta-galactosidase, gamma-glutamyl phosphate reductase, dihydrofolate reductase, lactate dehydrogenase, lysine, aminopeptidase pepS, fibronectin binding protein AB2, prolinase (pepR), Xaa-Pro dipeptidase and human bile salt export pump.

26. A method of identifying an organism or reproductive material or an extract therefrom as having a specific origin, the method comprising detecting in the genetic complement of the organism, material or extract the presence or absence of a polynucleotide identifier representative of said origin, the polynucleotide identifier comprising a sequence recited in SEQ ID NOS: 1-59.

27. The method of claim 26 wherein the organism is a bacterial cell or a yeast cell.

28. The method of claim 26 wherein the presence or absence of the polynucleotide identifier is detected by isolating DNA from the organism or material and contacting the isolated DNA with at least one oligonucleotide probe specific for the polynucleotide identifier.

29. The method of claim 26 wherein the isolated DNA is contacted with a plurality of oligonucleotide probes in an array format.

Figure 1. Nucleotide sequence containing *L. rhamnosus* strain HN001 fibronectin binding protein *AB2* showing putative ATG initiation and translation stop codons (boxed).

```
GTTATTTAGG CCCGAAAGTT TTATAAAAAA CGCGCGGNGC TTAACCTTAA GTCCCATTTT   60
GCGGGTTTGC CCCTCATTCC AAAAATATTG TTTCCTACCC GTGTTTGGTG AACGAACTTT  120
ATTGGGCCCT CCCCCATTTT ACACAGGCCG AATAAATTAA GGTTGTTTGA TCCCAAAAAA  180
TTGTGTAATG GTGAAGCGTT AAACCCCGGG CGGGTTTATT GTCCCAAAAT TTCCTTCTTA  240
AATTCCGGGC ATGTTCACGG TGGGCGGTTG ACCAGCCTTT GGCCTTAGGC GGCCTAAAAA  300
CCGGTAAAAT GATTGGGACA ATTGAAAAGC GAGCGGATCA ATATGTCTTT TGACGGAATT  360
TTTTCACCAT GCCAATGGCC CAGGAGCTTA ATACCACGTT AAGCGGCGGG CGGGTTGCTA  420
AAATTCAACA ACCTTATGAA AATGAAATTA TCATCACGAT TCGAGCTGGA CGCAAGAACC  480
ATCCCTTGTT GCTCTCAGCT AATCCACAGT ATGCGCGGGT GCAAATTACC CACATTCCAT  540
TTACAAATCC AGACGTTCCT GCAACCTTCA CGATGACGTT GCGGAAGTAT TTTAACGCGG  600
CTACGTTAAC AGAGATTCAC CAAGTGCAAA ACGATCGGGT ACTACACTTT GAATTCTCCA  660
CGCGGGATGA ATTGGGGGAT GAACTGGGGC TGCGCTTGAT CATTGAAATG ATGGGTCGGC  720
ACAGTAACAT CTTTTTAGTC AGCAAGCGCA CCGGCAAAAT TATTGATCTC ATTCGCCACG  780
TTTCTGCGGA TCAAAATCGC TATCGTCCGT TGATGCCCGG TGCCCCGTAT GTCGAGCCGC  840
CTAAGCAAGA TAAAGTGGAT CCGTTTCATG ATTCGGAGCG GATTTATCAC GAACTTGAAC  900
GTCAGGTAAC ACCTTCATTG AGTCGCGCCG CCTTGCTCCA GCAACATTAC CAAGGACTTG  960
CCAAGGATTC TGCAGCTGAA TTGGCCCTGC GACTCAATCA AGGCGATGCC GGCTGGGATA 1020
GCTTTTTTGC AGCGCTGGCA ACCCCTGAAC CGACTATTAC AACCCAAGGG AAAAAAGCCG 1080
TTTTTACCGC GATCCCGTAT CAGTCTCTGA CCGGCGAGCA GCAACATTTT CCAACCTTAA 1140
GCGCGATGCT GGATGCCTAT TATGCGCAAA AAGCGGAACA TGATCGGGTT TTGCAACAAG 1200
GCGGGAACCT GATTCATGTG ATCAAAAATG TGATTGATAA AGATCGCAAA AAGCAGCGCA 1260
AATTAAAGCG AACGCTGGAA GAAACCGAAA AAGCCGATGA TTATCGAATT CGCGGCGAGA 1320
TTCTGACGAC TTATCTGAGT CAAGTCAAAC GCGGCATGAC GAGTATTGAA CTGCCTAATT 1380
TCTATGCTGA TAATGAGCCA ATTAAGATCA CCTTGTCCAA TCAACTGACG CCATCACGCA 1440
ACGCCCAGAA ATATTTTGCC AAGTATACGA AATTACGCAA TGCAGTGGCG CATGTTCACC 1500
AGCAAATGCA GGAAAACCAA GAAGAACTCG ACTACCTTGA AGGCATCATG GCGCAGATTG 1560
ATGTAGCTAG TCCGAAAGAT TTAGTCGATA TTCGATTGGA ATTACAGCAA CAAGGCTATC 1620
TACGTAAACA GAAATCCGGA AAAAAAGGCA ATAAACGCCA AAAAGTCTCC AAACCAGATC 1680
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AGGTTAAAAA GATTCGTAAA CCTAATGGGG CCAAACCCGG CTTTGTCATT TACGAAGGCC 1980
AAAAAACAGT GAGTGTCACG CCTGACGCTG ATTTAGTCGC CAAGCTGCGT AACCCGCCGA 2040
CAAAATAGGA GATGTCTTTT CATGTCAGAA TCATCCGCCC AAATCAGCCG CCCACTTCAG 2100
GAACATATCA TTGCCAACAA AGTCAAACAT GG
```

Fig 2. The amino acid sequence of HN001 fibronectin binding protein AB2 showing the subcloned fibronectin binding domain (boxed).

MAQELNTTLS GGRVAKIQQP YENEIIITIR AGRKNHPLLL SANPQYARVQ 50
ITHIPFTNPD VPATFTMTLR KYFNAATLTE IHQVQNDRVL HFEFSTRDEL 100
GDELGLRLII EMMGRHSNIF LVSKRTGKII DLIRHVSADQ NRYRPLMPGA 150
PYVEPPKQDK VDPFHDSERI YHELERQVTP SLSRAALLQQ HYQGLAKDSA 200
AELALRLNQG DAGWDSFFAA LATPEPTITT QGKKAVFTAI PYQSLTGEQQ 250
HFPTLSAMLD AYYAQKAEHD RVLQQGGNLI HVIKNVIDKD RKKQRKLKRT 300
LEETEKADDY RIRGEILTTY LSQVKRGMTS IELPNFYADN EPIKITLSNQ 350
LTPSRNAQKY FAKYTKLRNA VAHVHQQMQE NQEELDYLEG IMAQIDVASP 400
KDLVDIRLEL QQQGYLRKQK SGKKGNKRQK VSKPDQFYAS DGTKIWVGKN 450
NLQNDQLTLH TAKKTDIWLH VKDIPGSHVI IDSSDPSEKT LLEAAKLAAY 500
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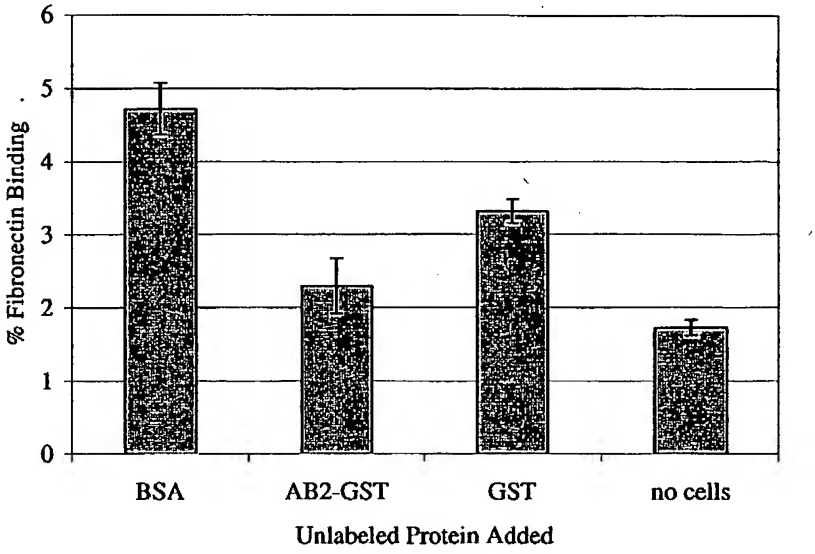
Fig. 3 Competition assay of iodine-125-labeled Fibronectin binding to HN001.



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Lubbers, Mark William
Dekker, James

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<212> DNA
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<210> 4
<211> 891
<212> DNA
<213> Lactobacillus rhamnosus

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<210> 5
<211> 1158
<212> DNA
<213> Lactobacillus rhamnosus

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<211> 786
<212> DNA
<213> Lactobacillus rhamnosus

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gccacgtcag cattgcaatc tgctgatgat gtgttggcac aggttcatgc tttcattcag 240
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accagtcagt caccggaatt taccgactat caacacatga atgttgttat caatccttca 480
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<210> 7
<211> 927
<212> DNA
<213> Lactobacillus rhamnosus

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<210> 8
<211> 810
<212> DNA
<213> Lactobacillus rhamnosus

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<210> 9
<211> 1425
<212> DNA
<213> Lactobacillus rhamnosus

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<210> 10
<211> 768
<212> DNA
<213> Lactobacillus rhamnosus

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<210> 11
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<212> DNA
<213> Lactobacillus rhamnosus

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aataatccag ttttaatcgg tgaagccggg gtcggcaaaa ccgcggttgt tgagggactg     180
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<210> 12
<211> 1443
<212> DNA
<213> Lactobacillus rhamnosus

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<212> DNA
<213> Lactobacillus rhamnosus
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<210> 14
<211> 1032
<212> DNA
<213> Lactobacillus rhamnosus

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<210> 15
<211> 1674
<212> DNA
<213> Lactobacillus rhamnosus

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<210> 16
<211> 876
<212> DNA
<213> Lactobacillus rhamnosus

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gaagttgcca gtcgtcacca tgtggaacag attacgttgg tgaccgatgc ggcattaaaa 240
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<210> 17
<211> 732
<212> DNA
<213> Lactobacillus rhamnosus

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gaaaacgagg ga 732

<210> 18
<211> 1299
<212> DNA
<213> Lactobacillus rhamnosus

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<210> 19
<211> 1344
<212> DNA
<213> Lactobacillus rhamnosus

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<210> 20
<211> 474
<212> DNA
<213> Lactobacillus rhamnosus

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<210> 21
<211> 1239
<212> DNA
<213> Lactobacillus rhamnosus

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<210> 22
<211> 1881
<212> DNA
<213> Lactobacillus rhamnosus

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<210> 23
<211> 606
<212> DNA
<213> Lactobacillus rhamnosus

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<210> 24
<211> 1023
<212> DNA
<213> Lactobacillus rhamnosus

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<210> 25
<211> 1227
<212> DNA
<213> Lactobacillus rhamnosus

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caagcttatg cccagttgca gaccaagcca actgatttgg ctaagcgtca atttttgatg 180
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<210> 26
<211> 1158
<212> DNA

<213> Lactobacillus rhamnosus

<220>
<221> misc_feature
<222> (1)...(1158)
<223> n = A,T,C or G

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aactggcgcg catcgtta 1158

<210> 27
<211> 1071
<212> DNA
<213> Lactobacillus rhamnosus

<400> 27
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aaaatggttt ggcaacgcgt gctggatcaa agggcgacag cgttgaatcg gcagggacga 180
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gggttaccgc ttgacaaagc ttttctctgg tcgcgcggtc acgttgccgg caatgagtat 360
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ccgcaaaatg ttgctgaaca attggcagaa tttcaaggaa aggagtcgaa g 1071

<210> 28
<211> 1310
<212> DNA

<213> Lactobacillus rhamnosus

<400> 28
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aaccacactt ttgctgtcag caccataata gcaaaagatg caactgtccg aatgaacgat 180
gtttccggac tgggtactgg taacatcagt aacgctggga cattatctct tactcatgcc 240
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ccgaaagcaa ccagtatgtg gatgcgccat gaaggaggac ataaccgctg gcgcgacggt 1260
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<210> 29
<211> 645
<212> DNA
<213> Lactobacillus rhamnosus

<400> 29
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gccgccgtta atcagtactt tgcggactat cagccagacg tggtgtatca ctgtgctgcc 180
tatacagccg ttgataaagc cgaagacgaa gcaaaagcgc tcaatcaatt ggtgaacgtt 240
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gcgccacgca atgaatatgg gcgggctaaa tacgaaggcg aacagcaggt gcaaaagtac 420
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caagaatctt tttccgtctc atcatcacgg acatttgtga aatatcaaca cgaacacctg 600
atttattccc gacctgtgcc atatcggccc caccttcctg gcata 645

<210> 30
<211> 1920
<212> DNA
<213> Lactobacillus rhamnosus

<220>
<221> misc_feature
<222> (1)...(1920)
<223> n = A,T,C or G

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gaaatgggga agaatattga tcggacctac atccagatgc gcatgctcaa cacgggtaaa     300
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aagagtattg tgctaacagc tggcaccagt tcccgcggta aaattattat cggcgaactc     540
atgtatagtt ccggccctaa caatagtctg ccaagcatta agctctctga aaatctggag     600
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<210> 31
<211> 762
<212> DNA
<213> Lactobacillus rhamnosus

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cggatgggtt acattgatcg cgatcaatta cgcaaactgg cgcagccgct taagaagaat     720
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<210> 32
<211> 936
<212> DNA
<213> Lactobacillus rhamnosus

<400> 32
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gctttatatg ccgttttggg gaaagaacac accgatcgcc taatggatcg cggcgtcatc 600
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aaacatgatt tacagctgca aaagcaaacg aaggag 936

<210> 33
<211> 840
<212> DNA
<213> Lactobacillus rhamnosus

<400> 33
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<210> 34
<211> 1341
<212> DNA
<213> Lactobacillus rhamnosus

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<210> 35
<211> 726
<212> DNA
<213> Lactobacillus rhamnosus

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agttactacg actcttatcg cgcccctgtt ctgccggcca acctgactca ggctcaacgc 660
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<210> 36
<211> 972
<212> DNA
<213> Lactobacillus rhamnosus

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<210> 37
<211> 888

<212> DNA
<213> Lactobacillus rhamnosus

<400> 37
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<210> 38
<211> 1422
<212> DNA
<213> Lactobacillus rhamnosus

<400> 38
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<210> 39
<211> 774
<212> DNA
<213> Lactobacillus rhamnosus

<400> 39

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gccagtggta aaaccggctt gggagttcct gaaattcttg agcgcatcgt ctcagacatt 180
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gggttcttgg gcctcttgca tatggatgtg gttcaggaac ggctggaacg cgattacggt 720
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<210> 40
<211> 1254
<212> DNA
<213> Lactobacillus rhamnosus

<400> 40
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<210> 41
<211> 489
<212> DNA
<213> Lactobacillus rhamnosus

<400> 41
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gtcgttggcc ggcgcaccta tgaaagtttt cctaaacgtc ctttacctga gcgaaccaat 180
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ggcagttttg aaggcgacac gaaaatgatt ccattaaact gggatgattt taccaaagtc 420
tccagccgca ccgttgaaga taccaatccg gcgctgacgc acacttatga ggtttggcaa 480
aagaaggct 489

<210> 42
<211> 285
<212> DNA
<213> Lactobacillus rhamnosus

<400> 42
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gacatctaca ttggtacacc tgctgtgatc aaccgcaatg gtattcagaa cattctggaa 180
atcccattga ccgaccacga agaagaatcc atgcagaagt cggcttcaca attgaagaaa 240
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<210> 43
<211> 969
<212> DNA
<213> Lactobacillus rhamnosus

<400> 43
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ttttccaag 969

<210> 44
<211> 1336
<212> DNA
<213> Lactobacillus rhamnosus

<400> 44
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cgctggttca ggatgt 1336

<210> 45
<211> 760
<212> DNA
<213> Lactobacillus rhamnosus

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<210> 46
<211> 1056
<212> DNA
<213> Lactobacillus rhamnosus

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<210> 47
<211> 1310

<212> DNA
<213> Lactobacillus rhamnosus

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<210> 48
<211> 1859
<212> DNA
<213> Lactobacillus rhamnosus

<400> 48
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<210> 49
<211> 887
<212> DNA
<213> Lactobacillus rhamnosus

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atgcctatta tgcgcaaaaa gcggaacatg atcgggtttt gcaacaaggc gggaacctga 780
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<210> 50
<211> 999
<212> DNA
<213> Lactobacillus rhamnosus

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<210> 51
<211> 846
<212> DNA

<213> Lactobacillus rhamnosus

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ttatcg 846

<210> 52
<211> 780
<212> DNA
<213> Lactobacillus rhamnosus

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ccatgagcat tagctggacg attatcggtg ctgcaagtcc gcgctgggct caaaaagttt 180
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aaggcgatga cgtcttacaa aacctgctaa aaacgccggg tgctcgttca ttaggcgaag 660
tgtcgttggt tccggatcct tcttccatct cacaatcggg ccttattttc ttcaatacgc 720
tggttgacga aaatgcttcc gatcatatgg cactcggtca agcctatccg ttctcagtca 780

<210> 53
<211> 1569
<212> DNA
<213> Lactobacillus rhamnosus

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gaaatcatcg cacaggatcc ggtccgcgta agcccgggga tgacgctggc acaattagaa 180
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cggcgggatg atcctgccca tatgcaggca ttggcagatc atgatattca gccaattgat 540
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gcgttaacc 1569

<210> 54
<211> 1112
<212> DNA
<213> Lactobacillus rhamnosus

<400> 54
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gtacttttca tccattttac caatccagac aacaagatgc ccgaatatca cacttgtttt 180
tacaaaactt tgaagttgtt ggcgtggttg ggttatggtt agggagtcat gaaaccgtca 240
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<210> 55
<211> 1570
<212> DNA
<213> Lactobacillus rhamnosus

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gcgtgatgct tgttggcaaa caggggtgcg gatccataca ttgatgttaa gcggccatcg 300
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taaggcgatt gatttggcta gtgatctggg cgttcgcaat gttcaactag ccggttatga 420
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gtttttgaat tcactttcca agatcaagac gattaaagat gagattccga gtccgtggtt 600
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tggtgttcct 1570

<210> 56
<211> 948
<212> DNA
<213> Lactobacillus rhamnosus

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<210> 57
<211> 1188
<212> DNA
<213> Lactobacillus rhamnosus

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<210> 58
<211> 1637
<212> DNA
<213> Lactobacillus rhamnosus

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<210> 59
<211> 2132
<212> DNA
<213> Lactobacillus rhamnosus

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gctttttgc agcgctggca acccctgaac cgactattac aacccaaggg aaaaaagccg 1080
tttttaccgc gatcccgtat cagtctctga ccggcgagca gcaacatttt ccaaccttaa 1140
gcgcgatgct ggatgcctat tatgcgcaaa aagcggaaca tgatcgggtt ttgcaacaag 1200
gcgggaacct gattcatgtg atcaaaaatg tgattgataa agatcgcaaa aagcagcgca 1260
aattaaagcg aacgctggaa gaaaccgaaa aagccgatga ttatcgaatt cgcggcgaga 1320
ttctgacgac ttatctgagt caagtcaaac gcggcatgac gagtattgaa ctgcctaatt 1380
tctatgctga taatgagcca attaagatca ccttgtccaa tcaactgacg ccatcacgca 1440
acgcccagaa atattttgcc aagtatacga aattacgcaa tgcagtggcg catgttcacc 1500
agcaaatgca ggaaaaccaa gaagaactcg actaccttga aggcatcatg gcgcagattg 1560
atgtagctag tccgaaagat ttagtcgata ttcgattgga attacagcaa caaggctatc 1620
tacgtaaaca gaaatccgga aaaaaaggca ataaacgcca aaaagtctcc aaaccagatc 1680
aattctatgc tagtgacggc actaaaatct gggtcggaaa aaacaactta caaaatgatc 1740
agttgaccct acacaccgcg aaaaaaaccg acatttggct gcacgtcaaa gatatcccgg 1800
gatcacacgt gattatcgat agcagtgatc ccagtgagaa aaccttgctg gaagcagcca 1860
agctggcagc gtatttttcc aaagcgcgcg acagtgccaa tgttccggtt gactggattg 1920
aggttaaaaa gattcgtaaa cctaatgggg ccaaacccgg ctttgtcatt tacgaaggcc 1980
aaaaaacagt gagtgtcacg cctgacgctg atttagtcgc caagctgcgt aacccgccga 2040
caaaatagga gatgtctttt catgtcagaa tcatccgccc aaatcagccg cccacttcag 2100
gaacatatca ttgccaacaa agtcaaacat gg 2132

<210> 60
<211> 38
<212> DNA
<213> Artificial sequence

<220>
<223> Made in the lab

<400> 60
ccgccgccgc tcgagaacgt tgcggaagta ttttaacg 38

<210> 61
<211> 39
<212> DNA
<213> Artificial Sequence

<220>
<223> Made in the lab

<400> 61
ccgccgccga agcttttatt gcttaggcgg ctcgacata 39

<210> 62
<211> 224
<212> PRT
<213> Lactobacillus rhamnosus

<400> 62
Leu Arg Gly Leu Cys Ile Gly Ile Val Ala Cys Glu Phe Phe Glu Ile
1 5 10 15
Pro Leu Thr Pro Ser Glu Ser Ala Asp Asn Gly Ile Gln Lys Arg Asn
20 25 30
Asp Val His Gln Trp Leu Val Ile Phe Arg Arg Asp Leu Leu Ala Asp
35 40 45
Leu Lys His Phe Asp Asn Gly Asp Arg Gly Ser Lys Gly Cys Val Phe
50 55 60
Asp Gln Ala Asp Glu Thr Ile Gln Trp Arg Asp Gly Arg Ser Cys Leu
65 70 75 80
Arg Asn Asn Asp Phe Ala Gln His Gln Ser Pro Arg Gln Ser Asn Cys
85 90 95
Ile Ser Arg Phe Pro Leu Pro Gly Ile Asn Arg Gln Gln Arg Gly Ala
100 105 110
Gly Arg Phe Gly Thr Ile Arg Pro Arg Val Lys Glu Cys Tyr Asn Ser
115 120 125
Arg Gly Arg Gly Ile Leu Asp Ala Met Arg Glu Asn Thr Arg Asp Asp
130 135 140
Glu Ala Gly Ala Glu Glu Asn Asp Glu Leu His Gln Gln Arg Arg Ala
145 150 155 160
Lys Glu Pro Asn Val Lys Asn Gly Asp Ser Phe Cys Asp Ser Asp Gln
165 170 175
Asn Thr Phe Thr Asn Arg Tyr Ala Arg Gln Cys Gly Tyr Lys Cys Asp
180 185 190
Asp Gln Ala Asp Arg Lys His Glu Cys Asn Trp Asn Gly Val Phe Asn
195 200 205
Ala Gly Cys Tyr His Leu Arg Asn Cys Ile Gly Asn Asn Phe Pro His
210 215 220

<210> 63
<211> 475
<212> PRT
<213> Lactobacillus rhamnosus

<400> 63
Leu Ile Cys Lys Gly Arg Ser Leu Lys Pro Phe Gly His Phe Ile Asp
1 5 10 15
Ala Ile Thr Val Asn Arg Glu His Val Leu Thr Thr Ala Ala Glu Ala
20 25 30
Leu Ile Ala Ser Ala Gly Asp Ala Leu Asn Ala Ser His Ala Thr Phe
35 40 45
Asn Val Leu Asn Asn Ser Asp Leu Gln Phe Gly Phe Val Glu Asn Glu
50 55 60
Asp Gly Glu Thr Val Gln Leu Ser Asn Gly Leu Tyr Gly Gln Leu Ile
65 70 75 80
Arg Ser Thr Asn Arg Lys Leu Arg Lys Glu Ala Phe Glu Ala Leu Leu
85 90 95
Arg Ala Tyr Glu Ser Leu Lys Asn Thr Phe Ala Gln Thr Leu Ser Gly

```
            100                 105                 110
Gln Val Lys Ala His Asn Phe Asn Ala Thr Ala His His Tyr Lys Asn
        115                 120                 125
Ala Arg Ala Ala Ala Met Ala Ser Asn His Ile Pro Glu Ser Val Tyr
    130                 135                 140
Thr Thr Leu Ile Asp Gln Val Asn Thr His Leu Pro Leu Leu His Arg
145                 150                 155                 160
Tyr Val Ala Leu Arg Lys Lys Val Leu Ala Val Asp Gln Leu His Met
                165                 170                 175
Tyr Asp Ile Tyr Thr Pro Leu Thr Gly Gln Pro Pro Leu Thr Tyr Thr
            180                 185                 190
Leu Glu Gln Ala Lys Ala Glu Ala Leu Lys Ala Leu Ala Pro Leu Gly
        195                 200                 205
Asp Asp Tyr Leu Glu His Val Arg Glu Ile Phe Asp Asn Arg Tyr Ile
    210                 215                 220
Asp Val Val Glu Asn Lys Gly Lys Arg Ser Gly Ala Tyr Ser Gly Gly
225                 230                 235                 240
Ala Tyr Asp Thr Asn Pro Phe Ile Leu Leu Asn Trp His Asp Ala Val
                245                 250                 255
Asp Glu Leu Tyr Thr Leu Val His Glu Thr Gly His Ser Val His Ser
            260                 265                 270
Trp Tyr Thr Arg His Asn Gln Pro Tyr Val Tyr Gly Asp Tyr Pro Ile
        275                 280                 285
Phe Val Ala Glu Ile Ala Ser Thr Thr Asn Glu Asn Leu Leu Thr Asp
    290                 295                 300
Tyr Phe Leu Thr His Ser Asp Asp Pro Lys Val Arg Ala Tyr Ile Leu
305                 310                 315                 320
Asn Tyr Tyr Leu Asp Gly Phe Lys Gly Thr Val Phe Arg Gln Thr Gln
                325                 330                 335
Phe Ala Glu Phe Glu His Trp Ile His Gln Gln Asp Gln Gln Gly Glu
            340                 345                 350
Pro Leu Thr Ala Thr Ser Met Ser Gln Tyr Tyr Ala Asp Leu Asn Ala
        355                 360                 365
Arg Tyr Tyr Gly Pro Glu Val Ala Arg Asp Pro Glu Ile Ala Phe Glu
    370                 375                 380
Trp Ala Arg Ile Pro His Phe Tyr Tyr Asn Tyr Tyr Val Tyr Gln Tyr
385                 390                 395                 400
Ala Thr Gly Phe Ala Ala Ala Ser Thr Leu Ala Ala Gly Ile Ser Ser
                405                 410                 415
Gly Glu Pro Asp Ala Ala Ala His Tyr Leu Asp Tyr Leu Lys Ser Gly
            420                 425                 430
Ser Ser Lys Tyr Ala Ile Asp Thr Met Lys Thr Ala Gly Val Asp Met
        435                 440                 445
Thr Lys Pro Asp Tyr Leu Glu Ala Ala Phe Ser Val Phe Glu Gln Arg
    450                 455                 460
Leu Thr Glu Leu Glu Lys Ile Leu Gln Lys Gly
465                 470                 475

<210> 64
<211> 345
<212> PRT
<213> Lactobacillus rhamnosus

<400> 64
Glu Glu Leu Gly Leu Pro Gln Leu Val Arg Met Ser Ala Asn Glu Asn
 1               5                  10                  15
Pro Phe Gly Thr Ser Val Lys Val Gln Gln Ala Val Thr Asn Trp Asn
```

```
            20                  25                  30
Phe Thr Gln Ser Arg Asp Tyr Pro Asp Gly Tyr Ala Ser Gln Leu Arg
        35                  40                  45
Thr Ala Val Ala Lys His Leu Asp Val Ala Ala Glu Gln Leu Val Phe
    50                  55                  60
Gly Asn Gly Leu Asp Glu Val Ile Ala Leu Ile Ala Arg Thr Phe Leu
65                  70                  75                  80
Ser Pro Gly Asp Glu Val Ile Glu Pro Trp Pro Thr Phe Ser Glu Tyr
                85                  90                  95
Arg Leu His Ala Gln Ile Glu Gly Ala Thr Val Ile Asp Val Pro Val
            100                 105                 110
Thr Glu Thr Gly Asn Phe Asp Leu Ser Ala Met Ala Gln Ala Leu Thr
        115                 120                 125
Ala Lys Thr Lys Leu Ile Trp Val Cys Asn Pro Asn Asn Pro Thr Gly
    130                 135                 140
Thr Leu Leu Ser Ile Ala Thr Leu Thr Glu Trp Leu Arg Gln Ile Pro
145                 150                 155                 160
Lys Asp Val Leu Val Leu Met Asp Glu Ala Tyr Ile Glu Phe Thr Asp
                165                 170                 175
Asp Tyr Pro Ala Thr Ser Ala Ile Ser Leu Leu Ser Lys Phe Pro Asn
            180                 185                 190
Leu Val Val Leu Arg Thr Phe Ser Lys Ile Tyr Gly Leu Ala Asn Phe
        195                 200                 205
Arg Val Gly Phe Gly Val Phe Pro Lys Gln Leu Val Asn Tyr Leu Gln
    210                 215                 220
Thr Val Arg Leu Pro Tyr Asn Leu Ser Ser Ile Ala Gln Val Ser Ala
225                 230                 235                 240
Gln Ala Ala Leu Ala Asp Gln Asp Phe Val Ala Met Thr Arg Lys Arg
                245                 250                 255
Val Gln Gln Ala Arg Asp Ser Trp Glu Arg Phe Leu Thr Gln Thr Gly
            260                 265                 270
Leu Pro His Thr Arg Ser Gln Thr Asn Phe Gln Phe Phe Gln Ala Pro
        275                 280                 285
Lys Met Gln Ala Ser Ala Leu Lys Lys Arg Leu Leu Gln Gln Gly Phe
    290                 295                 300
Leu Val Arg Asp Gly Leu Lys Pro Gly Trp Leu Arg Val Thr Phe Gly
305                 310                 315                 320
Thr Glu Val Gln Asn Thr Ala Val Gln Arg Ile Ile Glu Thr Phe Gln
                325                 330                 335
Ala Glu Leu Thr Gly Pro Asn Ala Leu
            340                 345

<210> 65
<211> 297
<212> PRT
<213> Lactobacillus rhamnosus

<400> 65
Val Ala Arg Leu Met Leu Asp Pro Gly Asp Gly Leu Val Val Glu Ala
 1               5                  10                  15
Pro Thr Tyr Leu Gly Ala Leu Ala Ala Phe Asn Ala Tyr Gln Pro Thr
            20                  25                  30
Tyr Tyr Glu Ile Pro Met Gln Asp Asp Gly Met Asp Ile Asn Ala Leu
        35                  40                  45
Gln Arg Val Leu Met Ser His Lys Val Lys Phe Ile Tyr Thr Val Pro
    50                  55                  60
Asp Phe Gln Asn Pro Thr Gly Val Val Met Ser Val Ala Lys Arg Gln
```

```
65                  70                  75                  80
Ala Leu Ile Arg Leu Ala Asn Gln Tyr Asp Val Met Ile Leu Glu Asp
                85                  90                  95
Asn Pro Tyr Arg Asp Leu Arg Tyr Asp Gly Lys Pro Leu Pro Thr Ile
            100                 105                 110
Lys Ser Phe Asp Thr Gln Gly Arg Val Val Tyr Leu Gly Ser Phe Ser
        115                 120                 125
Lys Ile Leu Ser Pro Ser Leu Arg Met Gly Trp Leu Val Ala Ala Pro
    130                 135                 140
Asp Leu Leu Gln Glu Leu Leu Ala Leu Lys Gly Gly Ser Asp Leu Glu
145                 150                 155                 160
Ser Ser Asn Leu Thr Met His Gly Ile Asp Ala Tyr Met Ala Glu Asn
                165                 170                 175
Asp Leu Asp Ala His Ile Thr Glu Ile Gln Asn Cys Cys Arg Glu Lys
            180                 185                 190
Lys Asn Ala Met Val Ala Ala Met Asn Arg Tyr Leu Pro Asp Glu Ala
        195                 200                 205
His Phe Thr Asn Pro Asp Gly Gly Phe Phe Leu Trp Leu Thr Met Pro
    210                 215                 220
Ala Gly Phe Asp Met Gly Ala Phe Met Lys Gln His Leu Leu Pro Glu
225                 230                 235                 240
Ser Asn Ile Ser Tyr Val Pro Ser Ala Asn Leu Tyr Ala Thr Ser Ala
                245                 250                 255
Gln Val Asn Gly Ala Arg Leu Asn Phe Thr Gly Pro Thr Leu Glu Gln
            260                 265                 270
Ile Asp Thr Gly Ile Lys Ala Leu Gly Asp Ala Leu Lys Thr Ala Leu
        275                 280                 285
Gln His His Leu Val Ala Glu Gln Ala
    290                 295
```

<210> 66
<211> 386
<212> PRT
<213> Lactobacillus rhamnosus

<220>
<221> VARIANT
<222> (1)...(386)
<223> Xaa = Any Amino Acid

<400> 66

```
Met Ile Tyr Phe Asp Asn Ser Ala Thr Thr Lys Ile Ser Pro Asp Ala
 1                5                  10                  15
Leu Ala Thr Tyr Asn Lys Val Ser Thr Asp Phe Phe Gly Asn Pro Ser
            20                  25                  30
Ser Leu His Ala Leu Gly Thr Lys Ala Asn Glu Val Leu Gln Ser Ser
        35                  40                  45
Arg Ala Gln Ile Ala Lys Leu Ile Gly Ala Lys Pro Asp Glu Ile Tyr
    50                  55                  60
Phe Thr Ser Gly Gly Thr Glu Arg Asp Asn Trp Val Xaa Leu Lys Gly
65                  70                  75                  80
Thr Ala Trp Leu Asn Ala Asn Leu Ala Arg Ile Leu Ile Thr Thr Ser
                85                  90                  95
Ile Glu Pro Pro Ala Val Ile Asn Thr Met Lys Gln Leu Glu Lys Leu
            100                 105                 110
Gly Phe Glu Val Thr Tyr Leu Pro Val Asp Arg Arg Gly Phe Ile His
        115                 120                 125
```

```
Ile Asp Asp Leu Lys Ala Ala Ile Arg Lys Asp Thr Ile Leu Val Ser
    130                 135                 140
Ile Met Ala Val Asn Asn Glu Ile Gly Ser Met Gln Pro Ile Val Gln
145                 150                 155                 160
Ala Ala Arg Val Leu Asp Asn Tyr Pro Asn Ile His Phe His Val Asp
                165                 170                 175
Ala Val Gln Ala Val Gly Lys Gly Leu Asp Ala Ala Leu Gln Asp Pro
            180                 185                 190
Arg Ile Asp Phe Leu Ser Phe Ser Gly His Lys Phe His Ala Pro Arg
        195                 200                 205
Gly Thr Gly Phe Ile Tyr Ala Lys Glu Gly Arg Met Leu Asp Pro Leu
    210                 215                 220
Leu Thr Gly Gly Gly Gln Glu His Asp Trp Arg Ser Gly Thr Glu Asn
225                 230                 235                 240
Val Pro Ala Ile Ala Ala Met Ala Lys Ser Leu Arg Leu Leu Leu Ala
                245                 250                 255
Asn Glu Asp Ala Asn Val Ala Arg Gln Gln Ala Val Arg Lys Arg Ile
            260                 265                 270
Phe Glu His Val Ser Gln Lys Pro Lys Val Thr Met Phe Ser Gln Leu
        275                 280                 285
Thr Pro Asp Phe Ala Pro His Val Leu Cys Phe Ala Ile Ala Gly Val
    290                 295                 300
Arg Gly Glu Thr Ile Val His Ala Phe Glu Asp His Gln Ile Tyr Ile
305                 310                 315                 320
Ser Thr Thr Ser Ala Cys Ser Ser Lys Lys Gly Thr Glu Ser Ser Thr
                325                 330                 335
Leu Ala Ala Met His Thr Asp Pro Lys Ile Ala Thr Ser Ala Ile Arg
            340                 345                 350
Val Ser Leu Asp Glu Ala Asn Thr Leu Asp Glu Ala Asp Ala Phe Asn
        355                 360                 365
Ala Ala Phe Asp Thr Ile Tyr Ala Lys Phe Ala Lys Leu Asp Lys Ala
    370                 375                 380
Thr Val
385
```

<210> 67
<211> 262
<212> PRT
<213> Lactobacillus rhammosus

<400> 67

```
Met Pro Thr Lys Ile Gly Leu His Tyr Asn Lys Ile Gly Val Gly Lys
 1               5                  10                  15
Thr Ile Tyr Phe Leu His Gly Met Gly Leu Asp Gly His Ser Met Ala
            20                  25                  30
Ala Phe Tyr Glu Pro Arg Phe Thr Ser Glu Glu Arg His Phe Ala Arg
        35                  40                  45
Leu Tyr Pro Asp Leu Pro Gly Met Gly Asn Ser Pro Ala Thr Ser Ala
    50                  55                  60
Leu Gln Ser Ala Asp Asp Val Leu Ala Gln Val His Ala Phe Ile Gln
65                  70                  75                  80
Ala Thr Ser Glu Gly Pro Cys Tyr Leu Val Gly His Ser Tyr Gly Gly
                85                  90                  95
Tyr Leu Ala Leu Gly Leu Leu Ala Arg Phe Pro Asp Glu Phe Ser Gly
            100                 105                 110
Ala Phe Leu Thr Ala Pro Val Val Leu Ala Glu Lys Thr Ala Arg Thr
        115                 120                 125
```

```
Val Ala Thr Leu Lys His Leu Ile Ser Ala Pro Val Thr Ser Gln Ser
    130                 135                 140
Pro Glu Phe Thr Asp Tyr Gln His Met Asn Val Val Ile Asn Pro Ser
145                 150                 155                 160
Thr Trp Arg Gln Tyr Gln Glu Leu Ile Leu Pro Gly Leu Lys Thr Phe
                165                 170                 175
Asn Arg Asp Phe Trp Val Ala Met Lys Asn Arg His Ala Tyr Arg Leu
            180                 185                 190
Ser Ile Glu Ser Arg Leu Thr Ser Leu Ile Lys Ser Pro Val Thr Leu
        195                 200                 205
Val Leu Gly Glu Asn Asp Asn Glu Val Gly Tyr Gln Asp Gln Val Val
    210                 215                 220
Phe Ala His Lys Gly Ala His Met Thr Thr Thr Val Ile Pro Asn Ala
225                 230                 235                 240
Gly His Asn Leu Met Ile Asp Ala Pro Glu Ala Val Met Thr Ala Phe
                245                 250                 255
His Gln Phe Leu His Lys
            260
```

<210> 68
<211> 309
<212> PRT
<213> Lactobacillus rhamnosus

```
<400> 68
Met Val Thr Ala Ala Asp Asn Ile Thr Gly Leu Ile Gly Asn Thr Pro
 1               5                  10                  15
Leu Leu Lys Leu Asn Arg Val Val Pro Glu Gly Ala Ala Asp Val Tyr
            20                  25                  30
Val Lys Leu Glu Phe Phe Asn Pro Gly Gly Ser Val Lys Asp Arg Ile
        35                  40                  45
Ala Leu Ala Met Ile Glu Asp Ala Glu Tyr Lys Gly Val Leu Lys Pro
    50                  55                  60
Gly Gly Thr Ile Val Glu Pro Thr Ser Gly Asn Thr Gly Ile Gly Leu
65                  70                  75                  80
Ala Leu Val Ala Ala Ala Lys Gly Tyr His Leu Ile Ile Thr Met Pro
                85                  90                  95
Glu Thr Met Ser Val Glu Arg Arg Ala Leu Met Arg Gly Tyr Gly Ala
            100                 105                 110
Glu Leu Ile Leu Thr Pro Gly Ala Asp Gly Met Pro Gly Ala Ile Lys
        115                 120                 125
Lys Ala Glu Ala Leu Ser Lys Glu Asn Gly Tyr Phe Leu Pro Met Gln
    130                 135                 140
Phe Gln Asn Pro Ala Asn Pro Asp Val His Glu Arg Thr Thr Gly Gln
145                 150                 155                 160
Glu Ile Ile Arg Ser Phe Asp Gly Gly Thr Pro Asp Ala Phe Val Ala
                165                 170                 175
Gly Val Gly Thr Gly Gly Thr Leu Thr Gly Val Gly Arg Ala Leu Arg
            180                 185                 190
Lys Ile Asn Pro Asp Val Gln Ile Tyr Ala Leu Glu Ala Ala Glu Ser
        195                 200                 205
Pro Met Leu Lys Glu Gly His Gly Gly Lys His Lys Ile Gln Gly Ile
    210                 215                 220
Ser Ala Gly Phe Ile Pro Asp Val Leu Asp Thr Asn Leu Tyr Gln Asp
225                 230                 235                 240
Ile Ile Glu Val Thr Ser Asp Gln Ala Ile Asp Met Ala Arg His Val
                245                 250                 255
```

```
Ser His Glu Glu Gly Phe Leu Pro Gly Ile Ser Ala Gly Ala Asn Ile
            260                 265                 270
Phe Gly Ala Ile Glu Ile Ala Lys Lys Leu Gly Lys Gly Lys Ser Val
        275                 280                 285
Ala Thr Val Ala Pro Asp Asn Gly Glu Arg Tyr Leu Ser Thr Asp Leu
    290                 295                 300
Phe Lys Phe Asp Asp
305
```

<210> 69
<211> 270
<212> PRT
<213> Lactobacillus rhamnosus

<400> 69

```
Met Leu Lys Lys Lys Leu Trp Phe Leu Leu Pro Leu Val Ala Leu Val
 1               5                  10                  15
Thr Phe Thr Leu Thr Ala Cys Thr Ser Ala Ser Ser Asp Thr Ser Lys
            20                  25                  30
Asn Ser Asp Val Thr Ala Glu Leu Ile Asn Lys Asn Glu Leu Thr Ile
        35                  40                  45
Gly Leu Glu Gly Thr Tyr Ala Pro Phe Ser Tyr Arg Lys Asp Gly Lys
    50                  55                  60
Leu Glu Gly Phe Glu Val Glu Leu Gly Lys Ala Leu Ala Lys Lys Ile
65                  70                  75                  80
Gly Val Lys Ala Lys Phe Val Pro Thr Gln Trp Asp Ser Leu Ile Ala
                85                  90                  95
Gly Leu Gly Ser Gln Lys Phe Asp Leu Val Leu Asn Asp Ile Ser Glu
            100                 105                 110
Thr Pro Ala Arg Lys Lys Val Tyr Asn Phe Thr Thr Pro Tyr Met Tyr
        115                 120                 125
Ser Arg Tyr Ala Leu Ile Thr Arg Ser Asp Asn Thr Thr Ile Lys Ser
    130                 135                 140
Leu Ala Asp Ile Lys Gly Lys Thr Phe Val Glu Gly Thr Gly Thr Pro
145                 150                 155                 160
Asn Ala Ala Leu Ala Lys Lys Tyr Gly Ala Lys Ile Thr Pro Ser Gly
                165                 170                 175
Asp Phe Thr Val Ser Leu Ser Leu Val Lys Glu Lys Arg Ala Asp Gly
            180                 185                 190
Thr Ile Asn Ala Ser Ala Ala Trp Tyr Ala Phe Ala Lys Asn Asn Ser
        195                 200                 205
Thr Ala Gly Leu Lys Ser Gln Thr Leu Lys Asp Ser Val Val Lys Pro
    210                 215                 220
Asp Glu Val Ala Gly Met Val Ser Lys Lys Ser Pro Lys Leu Gln Ala
225                 230                 235                 240
Ala Leu Ser Lys Gly Ile Gln Glu Leu Arg Lys Asp Gly Thr Leu Lys
                245                 250                 255
Lys Leu Ser Gln Lys Tyr Phe Gly Thr Asp Leu Thr Thr Lys
            260                 265                 270
```

<210> 70
<211> 474
<212> PRT
<213> Lactobacillus rhamnosus

<400> 70

```
Ile Cys Lys Gly Arg Ser Leu Lys Pro Phe Gly His Phe Ile Asp Ala
```

```
 1               5                  10                  15
Ile Thr Val Asn Arg Glu His Val Leu Thr Thr Ala Ala Glu Ala Leu
            20                  25                  30
Ile Ala Ser Ala Gly Asp Ala Leu Asn Ala Ser His Ala Thr Phe Asn
        35                  40                  45
Val Leu Asn Asn Ser Asp Leu Gln Phe Gly Phe Val Glu Asn Glu Asp
    50                  55                  60
Gly Glu Thr Val Gln Leu Ser Asn Gly Leu Tyr Gly Gln Leu Ile Arg
65                  70                  75                  80
Ser Thr Asn Arg Lys Leu Arg Lys Glu Ala Phe Glu Ala Leu Leu Arg
                85                  90                  95
Ala Tyr Glu Ser Leu Lys Asn Thr Phe Ala Gln Thr Leu Ser Gly Gln
            100                 105                 110
Val Lys Ala His Asn Phe Asn Ala Thr Ala His His Tyr Lys Asn Ala
        115                 120                 125
Arg Ala Ala Ala Met Ala Ser Asn His Ile Pro Glu Ser Val Tyr Thr
    130                 135                 140
Thr Leu Ile Asp Gln Val Asn Thr His Leu Pro Leu Leu His Arg Tyr
145                 150                 155                 160
Val Ala Leu Arg Lys Lys Val Leu Ala Val Asp Gln Leu His Met Tyr
                165                 170                 175
Asp Ile Tyr Thr Pro Leu Thr Gly Gln Pro Pro Leu Thr Tyr Thr Leu
            180                 185                 190
Glu Gln Ala Lys Ala Glu Ala Leu Lys Ala Leu Ala Pro Leu Gly Asp
        195                 200                 205
Asp Tyr Leu Glu His Val Arg Glu Ile Phe Asp Asn Arg Tyr Ile Asp
    210                 215                 220
Val Val Glu Asn Lys Gly Lys Arg Ser Gly Ala Tyr Ser Gly Gly Ala
225                 230                 235                 240
Tyr Asp Thr Asn Pro Phe Ile Leu Leu Asn Trp His Asp Ala Val Asp
                245                 250                 255
Glu Leu Tyr Thr Leu Val His Glu Thr Gly His Ser Val His Ser Trp
            260                 265                 270
Tyr Thr Arg His Asn Gln Pro Tyr Val Tyr Gly Asp Tyr Pro Ile Phe
        275                 280                 285
Val Ala Glu Ile Ala Ser Thr Thr Asn Glu Asn Leu Leu Thr Asp Tyr
    290                 295                 300
Phe Leu Thr His Ser Asp Asp Pro Lys Val Arg Ala Tyr Ile Leu Asn
305                 310                 315                 320
Tyr Tyr Leu Asp Gly Phe Lys Gly Thr Val Phe Arg Gln Thr Gln Phe
                325                 330                 335
Ala Glu Phe Glu His Trp Ile His Gln Gln Asp Gln Gln Gly Glu Pro
            340                 345                 350
Leu Thr Ala Thr Ser Met Ser Gln Tyr Tyr Ala Asp Leu Asn Ala Arg
        355                 360                 365
Tyr Tyr Gly Pro Glu Val Ala Arg Asp Pro Glu Ile Ala Phe Glu Trp
    370                 375                 380
Ala Arg Ile Pro His Phe Tyr Tyr Asn Tyr Tyr Val Tyr Gln Tyr Ala
385                 390                 395                 400
Thr Gly Phe Ala Ala Ala Ser Thr Leu Ala Ala Gly Ile Ser Ser Gly
                405                 410                 415
Glu Pro Asp Ala Ala Ala His Tyr Leu Asp Tyr Leu Lys Ser Gly Ser
            420                 425                 430
Ser Lys Tyr Ala Ile Asp Thr Met Lys Thr Ala Gly Val Asp Met Thr
        435                 440                 445
Lys Pro Asp Tyr Leu Glu Ala Ala Phe Ser Val Phe Glu Gln Arg Leu
    450                 455                 460
```

```
Thr Glu Leu Glu Lys Ile Leu Gln Lys Gly
465                 470

<210> 71
<211> 256
<212> PRT
<213> Lactobacillus rhamnosus

<400> 71
Ser Tyr Ala Pro Thr Ile Thr Leu Glu Gln Ala Lys Glu Asp Ile Lys
 1               5                  10                  15
Asn Ala Thr Ala Leu Met Gly Gln Asp Tyr Gln Ala Gln Met Met Gln
            20                  25                  30
Ala Phe Ser Glu Arg Trp Ile Asp Phe Pro Ala Asn Gln Gly Lys Asp
        35                  40                  45
Ser Gly Ala Tyr Thr Ala Gly Pro Tyr Gly Val His Pro Tyr Val Glu
    50                  55                  60
Met Thr Trp Ser Asn Thr Leu Pro Ala Val Tyr Thr Leu Ile His Glu
65                  70                  75                  80
Leu Gly His Thr Ala Gln Met Val Arg Ser Gln Glu Ala His Asn Val
                85                  90                  95
Leu Asp Ala Asp Phe Asn Ala Tyr Leu Val Glu Ser Pro Ser Thr Phe
            100                 105                 110
Asn Glu Leu Leu Leu Thr His Tyr Leu Glu Glu Asn Ala Lys Asp Pro
        115                 120                 125
Arg Met Lys Arg Phe Ala Leu Ser Arg Leu Leu Asn Asp Thr Tyr Phe
    130                 135                 140
His Asn Phe Val Thr His Leu Leu Glu Ala Ala Phe Gln Arg Glu Val
145                 150                 155                 160
Tyr Asn Leu Ile Asp Asn Gly Glu Thr Phe Asp Ala Ala Arg Leu Asn
                165                 170                 175
Ala Ile Thr Arg Lys Val Leu Thr Asp Phe Trp Gly Ser Ala Val Glu
            180                 185                 190
Leu Glu Pro Gly Ala Glu Leu Thr Trp Met Arg Gln Ser His Tyr Tyr
        195                 200                 205
Met Gly Leu Tyr Ser Tyr Ser Tyr Ser Ala Gly Leu Thr Val Ala Thr
    210                 215                 220
Gln Ala Phe Gln Ala Ile Glu Gln Gln Gly Gln Pro Ala Val Asp Arg
225                 230                 235                 240
Trp Leu Arg Tyr Leu Ser Leu Gly Asp Ser Leu Asp Pro Val Glu Ala
                245                 250                 255

<210> 72
<211> 641
<212> PRT
<213> Lactobacillus rhamnosus

<400> 72
Leu Leu Gly Gln Phe Gly Val Asp Leu Thr Glu Gln Ala Arg Lys Gly
 1               5                  10                  15
Gln Ile Asp Pro Val Ile Gly Arg Asp Lys Glu Ile Ser Arg Val Ile
            20                  25                  30
Glu Ile Leu Asn Arg Arg Thr Lys Asn Asn Pro Val Leu Ile Gly Glu
        35                  40                  45
Ala Gly Val Gly Lys Thr Ala Val Val Glu Gly Leu Ala Leu Lys Ile
    50                  55                  60
Ala Asn Gly Asp Val Pro Ala Lys Leu Gln Asp Arg His Val Ile Arg
```

```
65                  70                  75                  80
Leu Asp Val Val Ser Leu Val Gln Gly Thr Gly Ile Arg Gly Gln Phe
                85                  90                  95
Glu Gln Arg Met Gln Gln Leu Ile Asp Glu Leu Lys Gln Asn Lys Asn
            100                 105                 110
Ile Ile Leu Phe Ile Asp Glu Ile His Glu Ile Val Gly Ala Gly Asn
        115                 120                 125
Ala Glu Gly Gly Met Asp Ala Gly Asn Val Leu Lys Pro Ala Leu Ala
    130                 135                 140
Arg Gly Glu Leu Gln Leu Val Gly Ala Thr Thr Ser Asn Glu Tyr Arg
145                 150                 155                 160
Gln Ile Glu Lys Asp Ser Ala Leu Ala Arg Arg Leu Gln Pro Val Met
                165                 170                 175
Val Glu Glu Pro Ser Val Asp Glu Thr Ile Lys Ile Leu Lys Gly Leu
            180                 185                 190
Gln Pro Arg Tyr Gln Asp Phe His His Val Lys Tyr Thr Glu Gly Ala
        195                 200                 205
Ile Glu Ala Ala Ala Thr Leu Ser Asn Arg Tyr Ile Gln Asp Arg Phe
    210                 215                 220
Leu Pro Asp Lys Ala Ile Asp Leu Leu Asp Glu Ala Gly Ser Arg Lys
225                 230                 235                 240
Asn Leu Thr Ile Ala Thr Val Asp Pro Glu Thr Ile Lys Ala Lys Ile
                245                 250                 255
Ala Asp Ala Glu Lys Gln Lys Gln Ala Ala Leu Lys Gln Glu Asp Tyr
            260                 265                 270
Glu Lys Ala Ala Phe Tyr Arg Asp Gln Val Thr Lys Leu Glu Asp Met
        275                 280                 285
Ala Lys Lys Gln Ser Asn Leu Pro Asp Asn Glu Ile Pro Thr Val Thr
    290                 295                 300
Glu Lys Asp Met Glu Lys Ile Val Glu Glu Lys Thr Asn Ile Pro Val
305                 310                 315                 320
Gly Glu Leu Lys Ala Gln Glu Gln Ala Gln Leu Lys Asn Leu Ala Ser
                325                 330                 335
Asp Leu Glu Gln His Val Ile Gly Gln Asn Glu Ala Val Asp Lys Val
            340                 345                 350
Ala Arg Ala Ile Arg Arg Asn Arg Ile Gly Phe Asn Lys Thr Gly Arg
        355                 360                 365
Pro Ile Gly Ser Phe Leu Phe Val Gly Pro Thr Gly Val Gly Lys Thr
    370                 375                 380
Glu Leu Ala Lys Gln Leu Ala Lys Glu Leu Phe Gly Ser Glu Asp Ala
385                 390                 395                 400
Met Ile Arg Phe Asp Met Ser Glu Tyr Met Glu Lys Phe Ser Val Ser
                405                 410                 415
Lys Leu Ile Gly Ser Pro Pro Gly Tyr Val Gly Tyr Glu Glu Ala Gly
            420                 425                 430
Gln Leu Thr Glu Lys Val Arg Arg Asn Pro Tyr Ser Leu Ile Leu Leu
        435                 440                 445
Asp Glu Ile Glu Lys Ala His Pro Asp Val Met Asn Met Phe Leu Gln
    450                 455                 460
Ile Leu Asp Asp Gly Arg Leu Thr Asp Ser Gln Gly Arg Thr Val Ser
465                 470                 475                 480
Phe Lys Asp Thr Ile Ile Ile Met Thr Ser Asn Ala Gly Ser Thr Asp
                485                 490                 495
Ala Glu Ala Asn Val Gly Phe Gly Ala Thr Leu Ser Gly Lys Thr His
            500                 505                 510
Ser Val Leu Asp Gln Leu Gly Asn Tyr Phe Lys Pro Glu Phe Leu Asn
        515                 520                 525
```

```
Arg Phe Asp Asp Ile Val Glu Phe Lys Pro Leu Ser Lys Asp Asp Leu
    530                 535                 540
Leu Lys Ile Val Ser Leu Met Ile Asn Asp Thr Asn Asn Asn Leu Lys
545                 550                 555                 560
Ser Gln Gly Leu Thr Ile His Val Thr Asp Pro Val Lys Glu Lys Leu
                565                 570                 575
Val Thr Leu Gly Tyr Asn Pro Ser Met Gly Ala Arg Pro Leu Arg Arg
            580                 585                 590
Val Ile Gln Glu Gln Ile Glu Asp Arg Val Ala Asp Phe Tyr Leu Asp
        595                 600                 605
His Pro Asn Ala Lys Glu Leu Glu Ala Arg Ile Ser Asn Gly Glu Ile
    610                 615                 620
Thr Val Gly Glu Pro Ala Lys Ala Glu Ala Ser Ser Lys Thr Ala Lys
625                 630                 635                 640
Lys
```

<210> 73
<211> 481
<212> PRT
<213> Lactobacillus rhamnosus

<400> 73

```
Thr Lys Ser Val Val Gly Val Ala Pro Glu Ser Gln Leu Leu Ala Met
 1               5                  10                  15
Lys Val Phe Thr Asn Ser Asp Thr Ser Ala Thr Thr Gly Ser Ser Thr
            20                  25                  30
Leu Val Ser Ala Ile Glu Asp Ser Ala Lys Leu Gly Ala Asp Val Leu
        35                  40                  45
Asn Met Ser Leu Gly Ser Val Ser Gly Asn Gln Thr Leu Glu Asp Pro
    50                  55                  60
Glu Ile Ala Ala Val Gln Asn Ala Asn Glu Ser Gly Thr Ala Ala Val
65                  70                  75                  80
Ile Ser Ala Gly Asn Ser Gly Thr Ser Gly Ser Gly Thr Glu Gly Val
                85                  90                  95
Asn Lys Asp Tyr Tyr Gly Leu Gln Asp Asn Glu Thr Val Gly Thr Pro
            100                 105                 110
Gly Thr Ser Arg Gly Ala Thr Thr Val Ala Ser Ala Glu Asn Thr Asp
        115                 120                 125
Val Ile Asn Gln Ala Val Thr Ile Thr Asp Gly Ser Gly Leu Lys Leu
    130                 135                 140
Gly Pro Glu Thr Val Gln Leu Ser Ser Asn Asp Phe Val Asp Ser Phe
145                 150                 155                 160
Asp Gln Lys Lys Phe Tyr Val Val Lys Asp Ala Ser Gly Lys Leu Ser
                165                 170                 175
Thr Gly Asp Ala Gly Asp Tyr Thr Ala Asp Ala Lys Gly Lys Ile Ala
            180                 185                 190
Ile Val Lys Arg Gly Ser Leu Thr Phe Thr Asp Lys Gln Lys Tyr Ala
        195                 200                 205
Glu Ala Ala Gly Ala Ala Gly Leu Ile Ile Val Asn Asn Asp Gly Thr
    210                 215                 220
Ser Thr Pro Leu Thr Ser Ile Ser Leu Thr Ala Thr Phe Pro Thr Phe
225                 230                 235                 240
Gly Leu Ser Asn Thr Thr Gly Gln Lys Leu Val Asp Trp Val Thr Ala
                245                 250                 255
His Pro Asn Asp Ser Leu Gly Val Lys Ile Ala Leu Ala Leu Leu Pro
            260                 265                 270
```

```
Asn Gln Asn Tyr Lys Ala Asp Arg Met Ser Ser Phe Thr Ser Tyr Gly
        275                 280                 285
Pro Val Ser Asp Leu Ser Phe Lys Pro Asp Ile Thr Ala Pro Gly Gly
    290                 295                 300
Asn Ile Trp Ser Thr Gln Asn Asn Asn Gly Tyr Thr Asn Met Ser Gly
305                 310                 315                 320
Thr Ser Met Ala Ser Pro Phe Ile Ala Gly Ser Gln Ala Leu Leu Lys
                325                 330                 335
Gln Ala Leu Asn Asn Lys Asp Asn Glu Phe Tyr Ala Asp Tyr Lys Gln
            340                 345                 350
Leu Lys Gly Thr Ala Leu Thr Asp Phe Leu Lys Thr Val Glu Met Asn
        355                 360                 365
Thr Ala Lys Pro Ile Asn Asp Ile Asn Tyr Asp Asn Val Ile Val Ser
    370                 375                 380
Pro Arg Arg Gln Gly Ala Gly Leu Val Asp Val Lys Ala Ala Ile Asp
385                 390                 395                 400
Ala Leu Glu Lys Asn Pro Ser Thr Val Val Ser Glu Asn Gly Tyr Pro
                405                 410                 415
Ala Val Glu Leu Lys Asp Phe Thr Ser Thr Thr Lys Thr Phe Lys Leu
            420                 425                 430
Thr Phe Thr Asn Arg Thr Lys His Gln Leu Thr Tyr Gln Met Thr Ser
        435                 440                 445
Asn Glu Asp Thr Asn Ala Val Tyr Thr Ser Ala Thr Asp Leu Glu Ser
    450                 455                 460
Phe Ile Gln Ser Ser Lys Met Ala Lys Leu Ile His Glu Arg Gly Ala
465                 470                 475                 480
Ala
```

<210> 74
<211> 331
<212> PRT
<213> Lactobacillus rhamnosus

<400> 74

```
Met Thr Ile Asn Trp Gln Gln Glu Val Glu Lys Leu Glu Pro Gln Leu
 1               5                  10                  15
Leu Ser Asp Leu Thr Thr Leu Leu Lys Ile Asn Ser Glu Arg Asp Thr
            20                  25                  30
Asp His Gln Thr Asp Glu Tyr Pro Leu Gly Pro Gly Pro Ala Lys Ala
        35                  40                  45
Leu Glu Ala Phe Leu Ala Ile Ala Gln Arg Asp Gly Phe Lys Thr Leu
    50                  55                  60
Asn Val Asp His Val Ala Gly Arg Ile Glu Leu Gly Asp Gly Asp Glu
65                  70                  75                  80
Ile Phe Gly Leu Phe Gly His Val Asp Val Val Pro Ala Gly Pro Gly
                85                  90                  95
Trp Gln Thr Asp Pro Phe Asp Pro Val Ile Arg Asp Gly Lys Ile Tyr
            100                 105                 110
Gly Arg Gly Thr Ser Asp Asp Lys Gly Pro Ser Ile Ala Ala Tyr Tyr
        115                 120                 125
Ala Leu Lys Leu Ile Arg Asp Leu Lys Leu Pro Ile Asn Lys Lys Ile
    130                 135                 140
His Phe Ile Leu Gly Thr Asp Glu Glu Ser Asp Trp Val Gly Ile His
145                 150                 155                 160
Arg Tyr Leu Glu Thr Glu Pro Ala Pro Asp Phe Gly Phe Ser Pro Asp
                165                 170                 175
```

```
Ala Glu Phe Pro Ile Ile Asn Gly Glu Lys Gly Ile Ala Ser Phe Glu
            180                 185                 190
Ile Val Gln Lys Pro Ile Ala Ala Ala Thr Ala Asp Leu Thr Leu Asn
        195                 200                 205
His Phe Ser Ala Gly Ile Arg Pro Asn Met Val Pro Gln Glu Ala Lys
    210                 215                 220
Ala Val Leu Ser Gly Pro Leu Pro Glu Ala Phe Val Thr Gln Ala Glu
225                 230                 235                 240
Lys Trp Ala Ala Glu Gln Glu Val Thr Leu Thr Leu Thr Leu Gly Asn
                245                 250                 255
Pro Thr Thr Ile Glu Leu Ile Gly Lys Gly Ala His Ala Gln Glu Pro
            260                 265                 270
Lys Asp Gly Lys Asn Ala Ala Thr Tyr Leu Ala Thr Leu Leu Ala Asp
        275                 280                 285
Leu Pro Phe Asp Pro Ala Gly Lys Ala Tyr Leu Thr Met Ile Ala Asn
    290                 295                 300
His Leu His Leu Asp Ser Arg Gly His His Leu Gly Ile Asn Tyr Thr
305                 310                 315                 320
Asp Lys Leu Met Gly Asp Leu Thr Ala Ser Pro
                325                 330

<210> 75
<211> 344
<212> PRT
<213> Lactobacillus rhamnosus

<220>
<221> VARIANT
<222> (1)...(344)
<223> Xaa = Any Amino Acid

<400> 75
Gly Lys Met Ser Leu Tyr Ala Gly Gly Pro Asp Glu Arg Leu Thr Pro
 1                5                  10                  15
Leu Ile Asp Gly Arg Arg His Val Thr Asp Phe Ala Leu Thr Pro Asp
            20                  25                  30
His Arg Gly Val Val Phe Thr Glu Ser Thr Met Thr Ile Pro Ser Arg
        35                  40                  45
Leu Val Tyr Phe Asp Leu Ala Ser Glu Glu Glu Gln Val Leu Tyr Asp
    50                  55                  60
Pro Asn Arg Gln Val Thr Arg His Leu Gly Leu Val Thr Pro Gln Thr
65                  70                  75                  80
Phe Asn Phe Gln Arg Asp Gly Phe Glu Ile Glu Gly Trp Tyr Phe Pro
                85                  90                  95
Pro Gln Gln Ala Ser Ser Ser His Pro Ala Ile Leu Tyr Val His Gly
            100                 105                 110
Gly Pro Ala Val Gly Tyr Gly Tyr Thr Phe Phe His Glu Met Gln Tyr
        115                 120                 125
Leu Ala Ala Lys Gly Tyr Gly Val Ile Cys Arg Asn Pro Arg Gly Gly
    130                 135                 140
Leu Gly Tyr Arg Glu Ala Phe Thr Gly Ala Val Ile Lys His Xaa Pro
145                 150                 155                 160
Ala Gly Asp Tyr Glu Asp Cys Leu Ala Ser Gly Glu Glu Ala Leu Lys
                165                 170                 175
Leu Asp Thr Thr Ile Asp Pro Gln Arg Leu Phe Val Thr Gly Gly Ser
            180                 185                 190
Tyr Gly Gly Phe Met Thr Asn Trp Ile Val Thr His Thr His Arg Phe
```

```
        195                 200                 205
Lys Ala Ala Val Thr Gln Arg Ser Ile Ser Asn Trp Leu Ser Met Tyr
    210                 215                 220
Gly Thr Ser Asp Ile Gly Tyr Tyr Phe Thr Pro Trp Glu Leu Glu Gly
225                 230                 235                 240
Lys Trp Thr Gly Asp Leu Ser Asp Val Gln Gly Leu Trp Asp Phe Ser
                245                 250                 255
Pro Leu Ala His Ile Asp His Ala Arg Thr Pro Thr Leu Val Met His
            260                 265                 270
Ser Glu Asn Asp Glu Arg Cys Pro Ile Gly Pro Ser Arg Lys Val Asp
        275                 280                 285
His Arg Ser Gln Thr Ala Trp Cys Xaa Asn Gln Val His Ala Phe Pro
    290                 295                 300
Lys Val Lys Ser Xaa Phe Val Pro Ala Ala Gly Leu Pro Asn Leu Arg
305                 310                 315                 320
Val Ala Arg Leu Gln Ala Ile Val Asp Trp Phe Asp Ala His Gln Ala
                325                 330                 335
Gln Pro Gln Met Ala Lys Gly Glu
            340
```

<210> 76
<211> 558
<212> PRT
<213> Lactobacillus rhamnosus

<400> 76

```
His Leu Ile Gly Ala Thr Thr Leu Asp Glu Tyr Arg Glu Asn Ile Glu
 1               5                  10                  15
Lys Asp Lys Ala Leu Glu Arg Arg Phe Gln Arg Val Leu Val Gln Glu
            20                  25                  30
Pro Thr Val Glu Asp Thr Ile Ser Ile Leu Arg Gly Leu Lys Glu Arg
        35                  40                  45
Phe Glu Ile Phe His Lys Val Arg Ile His Asp Ser Ala Leu Val Ala
    50                  55                  60
Ala Ala Thr Leu Ser Asn Arg Tyr Ile Thr Asp Arg Phe Leu Pro Asp
65                  70                  75                  80
Lys Ala Ile Asp Leu Val Asp Glu Ala Cys Ala Thr Ile Asn Val Glu
                85                  90                  95
Met Asn Ser Arg Pro Thr Glu Leu Asp Val Ala Glu Arg Lys Gln Met
            100                 105                 110
Gln Leu Glu Ile Glu Gln Gln Ala Leu Lys Asn Glu Ser Asp Pro Ala
        115                 120                 125
Ser Lys Lys Arg Leu Glu Asn Ala Asn Ala Glu Leu Ala Asn Leu Lys
    130                 135                 140
Glu Lys Thr Asn Lys Leu Lys Ala Gln Trp Glu Ala Glu Lys Lys Asp
145                 150                 155                 160
Ile Arg Gln Leu Asn Glu Lys Lys Ser Ala Ile Asp Lys Ala Lys His
                165                 170                 175
Glu Leu Glu Asp Ala Gln Ser Arg Tyr Asp Leu Glu Thr Ala Ala Arg
            180                 185                 190
Leu Gln His Gly Thr Ile Pro Gln Leu Glu Lys Glu Leu Gln Ala Met
        195                 200                 205
Glu His Ser Asp Arg Pro Gln Ser Trp Leu Val Gln Glu Ser Val Thr
    210                 215                 220
Ala Asn Glu Ile Ala Ala Val Ile Ser Arg Glu Thr Gly Ile Pro Val
225                 230                 235                 240
Ala Lys Leu Val Glu Gly Asp Arg Gln Lys Leu Leu His Leu Ala Gly
```

```
                245                 250                 255
Asn Leu His Gln Arg Val Ile Gly Gln Asp Glu Ala Val Thr Ala Val
            260                 265                 270
Ser Asp Ala Val Leu Arg Ser Arg Ala Gly Leu Gln Asp Pro Ser Arg
        275                 280                 285
Pro Leu Gly Ser Phe Leu Phe Leu Gly Pro Thr Gly Val Gly Lys Thr
    290                 295                 300
Glu Leu Ala Lys Ala Leu Ala Glu Asp Leu Phe Asp Ser Glu Lys His
305                 310                 315                 320
Met Val Arg Ile Asp Met Ser Glu Tyr Met Glu Lys Ala Ser Val Ser
                325                 330                 335
Arg Leu Val Gly Ala Ala Pro Gly Tyr Val Gly Tyr Glu Gln Gly Gly
            340                 345                 350
Gln Leu Thr Glu Ala Val Arg Arg Asn Pro Tyr Thr Ile Val Leu Leu
        355                 360                 365
Asp Glu Ile Glu Lys Ala Asn Pro Asp Val Phe Asn Ile Leu Leu Gln
    370                 375                 380
Val Leu Asp Asp Gly Arg Leu Thr Asp Gly Gln Gly Arg Thr Val Asp
385                 390                 395                 400
Phe Lys Asn Thr Ile Ile Ile Met Thr Ser Asn Leu Gly Ser Glu Tyr
                405                 410                 415
Leu Leu Asp Gly Val Gln Lys Asp Gly Thr Val Ser Gln Gln Ala Lys
            420                 425                 430
Asp Gln Val Arg Gln Leu Ile Gly Lys Ala Phe Lys Pro Glu Phe Leu
        435                 440                 445
Asn Arg Ile Asp Asp Ile Ile Met Phe His Pro Leu Ser Leu Asp Asp
    450                 455                 460
Val Lys Lys Ile Ala Val Lys Asp Leu His Glu Leu Gly Thr Arg Leu
465                 470                 475                 480
Ala Asp Gln Gln Ile Ser Leu Asp Ile Thr Pro Glu Ala Gln Thr Trp
                485                 490                 495
Leu Ala Asp Lys Gly Tyr Asp Pro Ala Phe Gly Ala Arg Pro Leu Gln
            500                 505                 510
Arg Leu Ile Thr Ser Ala Val Glu Thr Pro Leu Ala Lys Glu Leu Ile
        515                 520                 525
Arg Gly Thr Ile Gln Pro Gly Gln Glu Val Val Ile Thr Val Ala Asp
    530                 535                 540
Asp Gln Leu Gln Phe Lys Ala Lys Gln Val Val Ala Lys Ala
545                 550                 555

<210> 77
<211> 292
<212> PRT
<213> Lactobacillus rhamnosus

<400> 77
Ile Ser Ala Ile Ile Val Ile Val Glu Glu Asn Asn Val Ala Ala Arg
 1               5                  10                  15
Glu Leu Ile Leu Ala Phe Glu Ser Ser Cys Asp Glu Thr Ser Val Ala
            20                  25                  30
Val Val Glu Asn Gly Thr Lys Ile Leu Ser Asn Ile Ile Ala Thr Gln
        35                  40                  45
Ile Lys Ser His Gln Arg Phe Gly Gly Val Val Pro Glu Val Ala Ser
    50                  55                  60
Arg His His Val Glu Gln Ile Thr Leu Val Thr Asp Ala Ala Leu Lys
65                  70                  75                  80
Glu Ala Gly Val Thr Tyr Thr Asp Leu Thr Ala Val Ala Val Thr Tyr
```

```
                85                  90                  95
Gly Pro Gly Leu Val Gly Ala Leu Leu Ile Gly Val Arg Ala Ala Lys
            100                 105                 110
Pro Ile Ala Tyr Ala His His Leu Pro Leu Ile Pro Val Asn His Met
        115                 120                 125
Ala Gly His Ile Tyr Ala Ala Arg Phe Val Lys Pro Leu Val Tyr Pro
    130                 135                 140
Leu Leu Ala Leu Ala Val Ser Gly Gly His Thr Glu Leu Val Tyr Met
145                 150                 155                 160
Arg Ala Ala Gly Glu Phe Glu Ile Ile Gly Asp Thr Arg Asp Asp Ala
                165                 170                 175
Ala Gly Glu Ala Tyr Asp Lys Val Gly Arg Ile Leu Gly Ile Pro Tyr
            180                 185                 190
Pro Ala Gly Lys Glu Val Asp Arg Leu Ala His Leu Gly His Asp Thr
        195                 200                 205
Phe His Phe Pro Arg Ala Met Asp Lys Glu Asp Asn Leu Asp Phe Ser
    210                 215                 220
Phe Ser Gly Leu Lys Ser Ala Val Ile Asn Thr Val His His Ala Asp
225                 230                 235                 240
Gln Ile Gly Glu Ser Leu Ser Arg Glu Asp Leu Ser Ala Ser Ser Gln
                245                 250                 255
Ala Ser Val Val His Val Met Val Leu Lys Ser Gln Ser Ala Ile Ala
            260                 265                 270
Glu Tyr Pro Val Ile Gln Val Val Ile Ala Gly Gly Val Ala Asp Asn
        275                 280                 285
Gln Gly Leu Lys
    290
```

<210> 78
<211> 244
<212> PRT
<213> Lactobacillus rhamnosus

<400> 78

```
Met Ile Phe Arg Lys Pro Gln Pro Phe Glu Tyr Glu Gly Thr Asp Thr
 1               5                  10                  15
Gly Val Val Leu Leu His Ala Tyr Thr Gly Ser Pro Asn Asp Met Asn
            20                  25                  30
Phe Met Ala Arg Ala Leu Gln Arg Ser Gly Tyr Gly Val Tyr Val Pro
        35                  40                  45
Leu Phe Ser Gly His Gly Thr Val Glu Pro Leu Asp Ile Leu Thr Lys
    50                  55                  60
Gly Asn Pro Asp Ile Trp Trp Ala Glu Ser Ser Ala Ala Val Ala His
65                  70                  75                  80
Met Thr Ala Lys Tyr Ala Lys Val Phe Val Phe Gly Leu Ser Leu Gly
                85                  90                  95
Gly Ile Phe Ala Met Lys Ala Leu Glu Thr Leu Pro Gly Ile Thr Ala
            100                 105                 110
Gly Gly Val Phe Ser Ser Pro Ile Leu Pro Gly Lys His His Leu Val
        115                 120                 125
Pro Gly Phe Leu Lys Tyr Ala Glu Tyr Met Asn Arg Leu Ala Gly Lys
    130                 135                 140
Ser Asp Glu Ser Thr Gln Ile Leu Ala Tyr Leu Pro Gly Gln Leu Ala
145                 150                 155                 160
Ala Ile Asp Gln Phe Ala Thr Thr Val Ala Ala Asp Leu Asn Leu Val
                165                 170                 175
Lys Gln Pro Thr Phe Ile Gly Gln Ala Gly Gln Asp Glu Leu Val Asp
```

```
            180                 185                 190
Gly Arg Leu Ala Tyr Gln Leu Arg Asp Ala Leu Ile Asn Ala Ala Arg
        195                 200                 205
Val Asp Phe His Trp Tyr Asp Asp Ala Lys His Val Ile Thr Val Asn
    210                 215                 220
Ser Ala His His Ala Leu Glu Glu Asp Val Ile Ala Phe Met Gln Gln
225                 230                 235                 240
Glu Asn Glu Gly
```

<210> 79
<211> 433
<212> PRT
<213> Lactobacillus rhamnosus

<400> 79

```
Leu Gly Ile Phe Phe Phe Lys Arg Phe Arg Lys Leu His Leu Phe Asp
 1               5                  10                  15
Pro Leu Asn Tyr Pro Glu Glu Thr Phe Gln Ser Phe Asp Ser Ala Phe
            20                  25                  30
Asn Asn Gly Ala Asp Tyr Val Glu Leu Asp Val His Glu Ser Ala Asp
        35                  40                  45
Gly Val Ile Val Ile Gln His Asp Thr Thr Ile Gln Arg Thr Thr Gly
    50                  55                  60
Ala Asn Leu Ala Ile Ala Lys Thr Asn Phe Ala Gln Leu Gln Gln Tyr
65                  70                  75                  80
His Thr Lys Asn Gly Glu Pro Ile His Ser Leu Glu Glu Leu Phe Ala
                85                  90                  95
His Glu Gln Gln Thr Lys His Lys Phe Leu Ile Glu Thr Lys Ile Val
            100                 105                 110
Lys Gly Glu Pro His Pro His Leu Glu Asp Lys Val Ala Ala Leu Ile
        115                 120                 125
Lys Gln Tyr His Met Glu Asn Arg Val Met Phe His Ser Phe Ser Ala
    130                 135                 140
Ala Ser Leu Lys Arg Leu Gln Ala Ala Leu Pro Asn Ile Pro Arg Ile
145                 150                 155                 160
Leu Ile Val Gly Ser Leu Lys Arg Ile Asn Phe Asp Val Leu Thr Tyr
                165                 170                 175
Val Asp Gly Ile Asn Leu Ser Ser Asp Leu Val Thr Pro Gln Leu Val
            180                 185                 190
Thr Gln Leu His Asp Leu Gly Lys Lys Val Tyr Val Trp Asp Glu Met
        195                 200                 205
Asn Glu Asp Arg Ala Lys Trp Thr Trp Leu Val Asn Leu Asn Ile Asp
    210                 215                 220
Gly Val Val Thr Asn Tyr Thr Ser Leu Gly His Glu Phe Gln Thr Leu
225                 230                 235                 240
Lys Ala Ala Ala Val Thr Thr Ser Ile Asn Asp Leu Gly Ala Asn Ser
                245                 250                 255
Ser Leu Ala Ala Leu Pro Val Tyr Glu Asn Pro Tyr Gln Pro Leu Leu
            260                 265                 270
Arg Ser Glu Arg Leu Ala Pro Gln Thr Pro Ile Met Ile Ser Ser Met
        275                 280                 285
Val Ser Leu Ala Gly Ser Thr Tyr Tyr Gln Ile Gly Asp Asn Ala Phe
    290                 295                 300
Val Pro Ala Glu Thr Ile Asn Leu Ala Pro Glu Ala Gly Trp Ala Ser
305                 310                 315                 320
Leu Phe Leu His Gln Arg Ile Val Ile Thr Ser Arg His Phe Lys Val
```

```
                325                 330                 335
Pro Val His Ala Asp Pro Leu His Gln Gln Ala Ile Thr Gly His Val
            340                 345                 350
Gly Asn His Lys Cys Tyr Arg Val Leu Ala Ala Arg Tyr Gln Ser Gly
        355                 360                 365
Gln Leu Tyr Leu Lys Thr Lys Ile Gly Trp Leu Asn Ala Lys Asp Leu
    370                 375                 380
Gln Val Leu Pro Thr Ala Glu Asn Met Arg Ile Trp Leu Thr Leu Tyr
385                 390                 395                 400
Arg Ser Ile Pro Glu Asn Gln Lys Pro Leu Leu His Trp Ala Leu Gly
                405                 410                 415
Asp Thr Ala Phe Asp Thr Pro Leu Leu Asn Ala Ser Val Leu Asn Ile
            420                 425                 430
Gly
```

<210> 80
<211> 448
<212> PRT
<213> Lactobacillus rhamnosus

<400> 80

```
Met Glu Leu Ala Lys Leu Ala Val Asp Glu Thr Gly Arg Gly Val Trp
 1               5                  10                  15
Glu Asp Lys Ala Ile Lys Asn Met Phe Ala Thr Glu Glu Ile Trp His
            20                  25                  30
Ser Ile Lys Asn Asn Lys Thr Val Gly Val Ile Asn Glu Asp Lys Gln
        35                  40                  45
Arg Gly Leu Val Ser Ile Ala Glu Pro Ile Gly Val Ile Ala Gly Val
    50                  55                  60
Thr Pro Val Thr Asn Pro Thr Ser Thr Thr Ile Phe Lys Ser Glu Ile
65                  70                  75                  80
Ser Ile Lys Thr Arg Asn Pro Ile Ile Phe Ala Phe His Pro Gly Ala
                85                  90                  95
Gln Lys Ser Ser Ala Arg Ala Leu Glu Val Ile Arg Glu Glu Ala Glu
            100                 105                 110
Lys Ala Gly Leu Pro Lys Gly Ala Leu Gln Tyr Ile Pro Val Pro Ser
        115                 120                 125
Met Glu Ala Thr Lys Thr Leu Met Asp His Pro Gly Ile Ala Thr Ile
    130                 135                 140
Leu Ala Thr Gly Gly Pro Gly Met Val Lys Ser Ala Tyr Ser Ser Gly
145                 150                 155                 160
Lys Pro Ala Leu Gly Val Gly Ala Gly Asn Ala Pro Ala Tyr Ile Glu
                165                 170                 175
Ala Ser Ala Asn Ile Lys Gln Ala Val Asn Asp Leu Val Leu Ser Lys
            180                 185                 190
Ser Phe Asp Asn Gly Met Ile Cys Ala Ser Glu Gln Gly Ala Ile Val
        195                 200                 205
Asp Ser Ser Ile Tyr Asp Ala Ala Lys Lys Glu Phe Glu Ala Gln Gly
    210                 215                 220
Ala Tyr Phe Val Lys Pro Lys Asp Met Lys Lys Phe Glu Ser Thr Val
225                 230                 235                 240
Ile Asn Leu Glu Lys Gln Ser Val Asn Pro Arg Ile Val Gly Gln Ser
                245                 250                 255
Pro Lys Gln Ile Ala Glu Trp Ala Gly Ile Arg Ile Pro Asp Asp Thr
            260                 265                 270
Thr Ile Leu Ile Ala Glu Leu Lys Asp Val Gly Lys Lys Tyr Pro Leu
```

```
        275                 280                 285
Ser Arg Glu Lys Leu Ser Pro Val Leu Ala Met Val Lys Ala Asp Gly
    290                 295                 300
His Glu Asp Ala Phe Lys Lys Cys Glu Thr Met Leu Asp Ile Gly Gly
305                 310                 315                 320
Leu Gly His Thr Ala Val Ile His Thr Ala Asp Asp Glu Leu Ala Leu
                325                 330                 335
Lys Phe Ala Asp Thr Met Gln Ala Cys Arg Ile Leu Ile Asn Thr Pro
            340                 345                 350
Ser Ser Val Gly Gly Ile Gly Asp Leu Tyr Asn Glu Met Ile Pro Ser
        355                 360                 365
Leu Thr Leu Gly Cys Gly Ser Tyr Gly Gly Asn Ser Ile Ser His Asn
    370                 375                 380
Val Gly Thr Val Asp Leu Leu Asn Ile Lys Thr Met Ala Lys Arg Arg
385                 390                 395                 400
Asn Asn Met Gln Trp Met Lys Leu Pro Pro Lys Ile Tyr Phe Glu Lys
                405                 410                 415
Asn Ser Val Arg Tyr Leu Glu His Met Glu Ser Ile Lys Arg Ala Phe
            420                 425                 430
Ile Val Ala Asp Arg Ser Met Glu Lys Ala Gly Phe Arg Gln Asp His
        435                 440                 445
```

<210> 81
<211> 158
<212> PRT
<213> Lactobacillus rhamnosus

<400> 81

```
Val Leu Val Asn Asn Ala Gly Ile Thr Asp Asp Met Leu Ala Met Arg
 1               5                  10                  15
Met Lys Pro Ala Ser Phe Ala Lys Val Val Gln Val Asn Leu Asp Gly
            20                  25                  30
Thr Phe Tyr Val Thr Gln Pro Ala Phe Lys Lys Met Leu Lys Ala Arg
        35                  40                  45
Ala Gly Val Ile Ile Asn Leu Ala Ser Val Val Gly Leu Thr Gly Asn
    50                  55                  60
Ile Gly Gln Ala Asn Tyr Ala Ala Ser Lys Ala Gly Ile Ile Gly Leu
65                  70                  75                  80
Thr Lys Thr Leu Ala Arg Glu Gly Ala Met Arg Gly Val Arg Val Asn
                85                  90                  95
Ala Ile Ala Pro Gly Met Ile Ala Thr Asp Met Thr Ala Ala Leu Ser
            100                 105                 110
Gln Ser Ser Gln Asp Gln Ile Leu Ala Glu Ile Pro Leu Lys Arg Phe
        115                 120                 125
Gly Gln Pro Glu Glu Ile Ala His Thr Ala Arg Phe Leu Val Glu Asn
    130                 135                 140
Ala Tyr Ile Thr Gly Gln Thr Val Thr Val Ala Gly Gly Leu
145                 150                 155
```

<210> 82
<211> 413
<212> PRT
<213> Lactobacillus rhamnosus

<400> 82

```
Ala Val Ala Leu Pro Leu Leu Gly Val Leu Ala Ile Ala Ala Thr His
 1               5                  10                  15
```

```
Ala Glu Gly Val Tyr Asp Ile Gly Arg Pro Leu Gly Arg Phe Phe Ala
            20                  25                  30
Leu Ala Phe Met Val Leu Ile His Ala Thr Ile Gly Pro Met Phe Gly
        35                  40                  45
Thr Pro Arg Thr Ala Thr Val Ser Phe Thr Thr Gly Val Leu Pro Met
    50                  55                  60
Leu Pro Lys Ala Trp Gln Gln Gly Gly Leu Leu Val Phe Ser Ala Leu
65                  70                  75                  80
Phe Phe Gly Ala Ala Phe Phe Leu Ser Tyr Lys Glu Arg Lys Ile Thr
                85                  90                  95
Thr Ala Val Gly Lys Val Leu Asn Pro Val Phe Leu Leu Leu Leu Phe
            100                 105                 110
Phe Val Phe Phe Ile Gly Phe Leu His Pro Met Gly Asn Pro Ala Ala
        115                 120                 125
Gln Thr Val Thr Ala Ala Tyr Lys Asn Gly Gly Ser Phe Met Ser Gly
    130                 135                 140
Phe Leu Gln Gly Tyr Asn Thr Met Asp Ala Leu Ala Ala Leu Ala Phe
145                 150                 155                 160
Gly Val Thr Val Val Thr Ala Val Arg Gly Leu Gly Leu Lys Asn Asp
                165                 170                 175
Asp His Val Ala Lys Ala Thr Ala Lys Ala Gly Val Met Ala Thr Ser
            180                 185                 190
Trp Ile Ala Leu Ile Tyr Val Ala Leu Ile Val Leu Gly Ser Met Ser
        195                 200                 205
Leu Ala His Phe Lys Leu Ser Ala Glu Gly Gly Thr Ala Phe Asn Gln
    210                 215                 220
Val Gly Thr Phe Tyr Phe Gly Thr Val Gly His Pro Ala Trp Gln Pro
225                 230                 235                 240
Cys Leu Thr Leu Thr Cys Leu Asn Thr Pro Val Gly Phe Val Arg Ala
                245                 250                 255
Phe Pro His Asp Phe His Arg His Phe Pro Lys Val Ser Tyr Gln Val
            260                 265                 270
Trp Leu Gly Leu Thr Ser Phe Leu Ser Phe Leu Thr Ala Asn Phe Gly
        275                 280                 285
Leu Glu Gln Ile Ile Ala Trp Ser Val Pro Met Leu Met Phe Leu Tyr
    290                 295                 300
Pro Phe Ser Met Val Leu Ile Leu Leu Ser Val Phe Gly Lys Ala Phe
305                 310                 315                 320
His His Asp Pro Leu Val Tyr Arg Ile Val Val Ala Phe Thr Ile Val
                325                 330                 335
Pro Ala Val Leu Asp Met Phe Ala Ala Phe Pro Ala Val Val Ser Gln
            340                 345                 350
Ser Ser Leu Gly Leu Ala Leu His Ser Phe Gln Leu His Phe Leu Pro
        355                 360                 365
Phe Ser Ala Met Gly Leu Gly Trp Leu Val Pro Ala Gly Val Gly Leu
    370                 375                 380
Val Leu Gly Leu Val Ala His Ala Val Lys Val Arg Lys Ala Val Ala
385                 390                 395                 400
Ala Thr His Leu Glu Ala Glu Gln Thr Gln Leu Val His
                405                 410
```

<210> 83
<211> 627
<212> PRT
<213> Lactobacillus rhamnosus

<400> 83

```
Met Ala Asp Asn His Lys Ala Gln Thr Thr Lys Gln Pro Ser Gly Pro
 1               5                  10                  15
Arg Met Gly Pro Gly Arg Gly Gly Leu Val Glu Lys Pro Lys Asn Phe
            20                  25                  30
Trp Gly Thr Thr Ala Arg Leu Phe Gly Tyr Met Arg Asn Arg Leu Ile
        35                  40                  45
Gly Ile Ile Ala Val Leu Val Leu Ala Ile Ala Ser Thr Val Phe Gln
    50                  55                  60
Ile Arg Thr Pro Lys Ile Leu Gly Glu Ala Thr Thr Glu Ile Phe Lys
65                  70                  75                  80
Gly Val Met Lys Gly Gln Ala Glu Gln Lys Ala Gly Ile Ala Val Gly
                85                  90                  95
Asn Tyr Pro Ile Asp Phe Asp Lys Ile Lys Gln Ile Ile Leu Ile Val
            100                 105                 110
Leu Val Leu Tyr Leu Gly Ser Ala Leu Phe Ser Phe Leu Gln Gln Phe
        115                 120                 125
Ile Met Thr Arg Ile Ser Gln Asn Thr Val Tyr Gln Leu Arg Lys Asp
    130                 135                 140
Leu Lys His Lys Met Lys Thr Val Pro Ile Lys Tyr Tyr Asp Thr His
145                 150                 155                 160
Ser Asn Gly Asp Ile Met Ser Arg Ala Ile Asn Asp Met Asp Asn Ile
                165                 170                 175
Ala Ser Thr Leu Gln Gln Ser Leu Thr Gln Met Val Thr Ser Ala Val
            180                 185                 190
Met Phe Val Gly Thr Ile Trp Met Met Leu Thr Ile Ser Trp Lys Leu
        195                 200                 205
Thr Leu Ile Ala Leu Val Thr Ile Pro Leu Gly Leu Ile Val Val Gly
    210                 215                 220
Ile Val Ala Pro Lys Ser Gln Arg Phe Phe Ala Ala Gln Gln Lys Ala
225                 230                 235                 240
Leu Gly Leu Leu Asn Asn Gln Val Glu Glu Thr Tyr Gly Gly Gln Val
                245                 250                 255
Ile Ile Lys Ser Phe Asn Arg Glu Asp Asp Glu Val Glu Ala Phe Glu
            260                 265                 270
Gly Gln Asn Gln Ala Phe Tyr Asp Ala Ala Trp Lys Ala Gln Phe Val
        275                 280                 285
Ser Gly Ile Ile Met Pro Leu Met Ile Phe Leu Asn Asn Ile Gly Tyr
    290                 295                 300
Val Phe Val Ala Ile Met Gly Gly Ile Glu Val Ser Asn Gly Thr Ile
305                 310                 315                 320
Thr Leu Gly Asn Val Gln Ala Phe Leu Gln Tyr Met Gln Gln Phe Ser
                325                 330                 335
Gln Pro Ile Ser Gln Leu Ala Asn Leu Ala Asn Thr Ile Gln Ser Thr
            340                 345                 350
Ile Ala Ser Ala Glu Arg Ile Phe Ala Val Leu Asp Glu Glu Asp Met
        355                 360                 365
Gln Asp Glu Pro Ser Gly Val Pro Ala Val Ala Asn Asp Pro Asn Lys
    370                 375                 380
Leu Val Met Asp His Val Gln Phe Gly Tyr Thr Pro Asp Ala Leu Leu
385                 390                 395                 400
Leu Lys Asp Tyr Asn Leu Gln Val Lys Pro Gly Glu Met Val Ala Ile
                405                 410                 415
Val Gly Pro Thr Gly Ala Gly Lys Thr Thr Ile Ile Asn Leu Leu Glu
            420                 425                 430
Arg Phe Tyr Asp Ile Ser Gly Gly Ser Ile Arg Leu Asn Gly Thr Asp
        435                 440                 445
Thr Arg Asp Met Lys Arg Glu Asp Val Arg Ala His Phe Ala Met Val
```

```
    450                 455                 460
Leu Gln Asp Thr Trp Leu Phe Thr Gly Thr Ile Trp Asp Asn Leu Lys
465                 470                 475                 480
Tyr Gly Arg Glu Asp Ala Thr Asp Asp Glu Val Leu Ala Ala Ala Lys
                485                 490                 495
Ala Ala His Val Asp Asn Phe Val Arg Gln Leu Pro Asp Gly Tyr Asn
            500                 505                 510
Thr Ile Leu Asn Glu Glu Ala Ser Asn Ile Ser Gln Gly Gln Arg Gln
        515                 520                 525
Leu Leu Thr Ile Ala Arg Ala Phe Val Ala Asp Pro Glu Ile Leu Ile
    530                 535                 540
Leu Asp Glu Ala Thr Ser Ser Val Asp Thr Arg Thr Glu Ile His Ile
545                 550                 555                 560
Gln His Ala Met Asn Arg Leu Leu Thr Asp Arg Thr Ser Phe Val Val
                565                 570                 575
Ala His Arg Leu Ser Thr Ile Arg Asp Ala Asp Lys Ile Ile Val Met
            580                 585                 590
Asn His Gly Ser Ile Val Glu Thr Gly Asn His Asp Glu Leu Met Ala
        595                 600                 605
Lys Asn Gly Phe Tyr Ala Asp Leu Tyr Asn Ser Gln Phe Ser Gly Asn
    610                 615                 620
Val Ala Ile
625
```

<210> 84
<211> 202
<212> PRT
<213> Lactobacillus rhamnosus

```
<400> 84
Thr Thr Arg Leu Ser Ser Leu Ile Thr Glu Tyr Leu Asp Ser Gln Leu
 1               5                  10                  15
Ala Glu Arg Arg Ser Met His Gly Val Leu Val Asp Ile Tyr Gly Leu
            20                  25                  30
Gly Val Leu Ile Thr Gly Asp Ser Gly Val Gly Lys Ser Glu Thr Ala
        35                  40                  45
Leu Glu Leu Val Gln Arg Gly His Arg Leu Ile Ala Asp Asp Arg Val
    50                  55                  60
Asp Val Tyr Gln Gln Asp Glu Gln Thr Val Val Gly Ala Ala Pro Pro
65                  70                  75                  80
Ile Leu Ser His Leu Leu Glu Ile Arg Gly Leu Gly Ile Ile Asp Val
                85                  90                  95
Met Asn Leu Phe Gly Ala Gly Ala Val Arg Glu Asp Thr Thr Ile Ser
            100                 105                 110
Leu Ile Val His Leu Glu Asn Trp Thr Pro Asp Lys Thr Phe Asp Arg
        115                 120                 125
Leu Gly Ser Gly Glu Gln Thr Gln Met Ile Phe Asp Val Pro Val Pro
    130                 135                 140
Lys Ile Thr Ile Pro Val Lys Val Gly Arg Asn Leu Ala Ile Ile Ile
145                 150                 155                 160
Glu Val Ala Ala Met Asn Phe Arg Ala Lys Ser Met Gly Tyr Asp Ala
                165                 170                 175
Thr Lys Thr Phe Glu Lys Asn Leu Asn His Leu Ile Glu His Asn Glu
            180                 185                 190
Ala Asn Asp Gln Lys Ser Ser Glu Glu Lys
        195                 200
```

<210> 85
<211> 341
<212> PRT
<213> Lactobacillus rhamnosus

<220>
<221> VARIANT
<222> (1)...(341)
<223> Xaa = Any Amino Acid

<400> 85
Met Ser Ile Ser Thr Arg Ala Asn Lys Leu Asp Gly Val Glu Gln Ala
1 5 10 15
Xaa Val Ala Met Ala Thr Glu Met Asn Lys Gly Val Leu Lys Asn Leu
20 25 30
Gly Leu Leu Thr Pro Glu Leu Glu Gln Ala Lys Asn Gly Asp Leu Met
35 40 45
Ile Val Ile Asn Gly Lys Ser Gly Ala Asp Asn Glu Gln Leu Leu Val
50 55 60
Glu Ile Glu Glu Leu Phe Asn Thr Lys Ala Gln Ser Gly Ser His Glu
65 70 75 80
Ala Arg Tyr Ala Thr Ile Gly Ser Ala Lys Lys His Ile Pro Glu Ser
85 90 95
Asn Leu Ala Val Ile Ser Val Asn Gly Leu Phe Ala Ala Arg Glu Ala
100 105 110
Arg Gln Ala Leu Gln Asn Asp Leu Asn Val Met Leu Phe Ser Asp Asn
115 120 125
Val Ser Val Glu Asp Glu Leu Ala Leu Lys Gln Leu Ala His Glu Lys
130 135 140
Gly Leu Leu Met Met Gly Pro Asp Cys Gly Thr Ala Ile Ile Asn Gly
145 150 155 160
Ala Ala Leu Cys Phe Gly Asn Ala Val Arg Arg Gly Asn Ile Gly Ile
165 170 175
Val Gly Ala Ser Gly Thr Gly Ser Gln Glu Leu Ser Val Arg Ile His
180 185 190
Glu Phe Gly Gly Gly Val Ser Gln Leu Ile Gly Thr Gly Gly Arg Asp
195 200 205
Leu Ser Glu Lys Ile Gly Gly Leu Met Met Leu Asp Ala Ile Gly Met
210 215 220
Leu Glu Asn Asp Pro Gln Thr Glu Ile Ile Ala Leu Ile Ser Lys Pro
225 230 235 240
Pro Ala Pro Ala Val Ala Arg Lys Val Leu Glu Arg Ala Arg Ala Cys
245 250 255
Arg Lys Pro Val Val Val Cys Phe Leu Asp Arg Gly Glu Thr Pro Val
260 265 270
Asp Glu Gln Gly Leu Gln Phe Ala Arg Gly Thr Lys Glu Ala Ala Leu
275 280 285
Lys Ala Val Met Leu Ser Gly Val Lys Gln Glu Asn Leu Asp Leu His
290 295 300
Thr Leu Asn Gln Pro Leu Ile Ala Asp Val Arg Ala Arg Leu Gln Pro
305 310 315 320
Gln Gln Lys Tyr Ile Arg Gly Leu Ser Ala Ala Ala Arg Cys Ala Thr
325 330 335
Lys Pro Cys Ser Arg
340

<210> 86

<211> 409
<212> PRT
<213> Lactobacillus rhamnosus

<400> 86
Gln Ile Leu Asn Asn Pro Phe Leu Asn Lys Gly Thr Ala Phe Thr Gln
1 5 10 15
Glu Glu Arg Asn Gln Tyr Gly Leu Asn Gly Leu Leu Pro Pro Ala Val
20 25 30
Gln Thr Leu Asp Gln Gln Val Lys Gln Ala Tyr Ala Gln Leu Gln Thr
35 40 45
Lys Pro Thr Asp Leu Ala Lys Arg Gln Phe Leu Met Thr Leu Phe Asn
50 55 60
Glu Asn His Val Leu Phe Tyr Lys Leu Phe Ser Glu His Ile Asn Glu
65 70 75 80
Phe Met Pro Ile Val Tyr Asp Pro Thr Ile Ala Asp Thr Ile Glu Asn
85 90 95
Tyr Ser Ala Leu Phe Val Asn Pro Gln Asn Ala Thr Tyr Leu Ser Ile
100 105 110
Asp Asp Pro Asp His Ile Glu Ser Ala Leu Lys His Ser Ala Asp Gly
115 120 125
Arg Asp Ile Arg Leu Leu Val Val Ser Asp Ala Glu Gly Ile Leu Gly
130 135 140
Ile Gly Asp Trp Gly Thr Gln Gly Val Asp Ile Ser Val Gly Lys Leu
145 150 155 160
Met Val Tyr Thr Ala Ala Ala Gly Ile Asp Pro Ser Gln Val Leu Pro
165 170 175
Val Val Leu Asp Val Gly Thr Asn Asn Glu Gly Leu Leu Asn Asp Asp
180 185 190
Leu Tyr Leu Gly Asn Arg His Lys Arg Val Tyr Gly Glu Lys Tyr His
195 200 205
His Phe Val Asp Lys Phe Val Ala Ala Ala Glu Lys Leu Phe Pro Asn
210 215 220
Leu Tyr Leu His Phe Glu Asp Phe Gly Arg Ser Asn Ala Ala Asp Ile
225 230 235 240
Leu Asn Gln Tyr Lys Asp Lys Ile Thr Thr Phe Asn Asp Asp Ile Gln
245 250 255
Gly Thr Gly Ile Ile Val Leu Ala Gly Leu Leu Gly Ala Met Asn Ile
260 265 270
Ser Lys Gln Lys Leu Thr Asp Gln Val Tyr Leu Ser Phe Gly Ala Gly
275 280 285
Thr Ala Gly Ala Gly Ile Ala Ser Arg Val Tyr Glu Ala Phe Val Glu
290 295 300
Glu Gly Leu Ser Pro Glu Glu Ala Lys Lys His Phe Tyr Leu Val Asp
305 310 315 320
Lys Gln Gly Leu Leu Phe Asp Asp Met Thr Asp Leu Thr Pro Glu Gln
325 330 335
Lys Pro Phe Ala Arg Ser Arg Ser Glu Phe Ala Asn Ala Asp Glu Leu
340 345 350
Thr Thr Leu Glu Ala Val Val Lys Ala Val His Pro Thr Val Leu Val
355 360 365
Gly Thr Ser Thr Val Pro Gly Thr Phe Thr Glu Ser Ile Val Lys Glu
370 375 380
Met Ala Ala His Thr Asp Arg Pro Ile Ile Phe Pro Leu Ser Asn Pro
385 390 395 400
Thr Lys Leu Ala Glu Ala Lys Ala Asp
405

<210> 87
<211> 386
<212> PRT
<213> Lactobacillus rhamnosus

<220>
<221> VARIANT
<222> (1)...(386)
<223> Xaa = Any Amino Acid

<400> 87.

```
Met Ile Lys Pro Glu Lys Thr Ile Asn Gly Thr Lys Trp Ile Glu Thr
 1               5                  10                  15
Ile Gln Ile Asn Ala Glu Glu Arg Ala Thr Leu Glu Asp Gln Tyr Gly
            20                  25                  30
Val Asp Glu Asp Ile Ile Glu Tyr Val Thr Asp Asn Asp Glu Ser Thr
        35                  40                  45
Asn Tyr Val Tyr Asp Ile Asn Glu Asp Asp Gln Leu Phe Ile Phe Leu
    50                  55                  60
Ala Pro Tyr Ala Leu Asp Lys Asp Ala Leu Arg Tyr Ile Thr Gln Pro
65                  70                  75                  80
Phe Gly Met Leu Leu His Lys Gly Val Leu Phe Thr Phe Asn Gln Ser
                85                  90                  95
His Ile Pro Glu Val Asn Thr Ala Leu Tyr Ser Ala Leu Asp Asn Pro
            100                 105                 110
Glu Val Lys Ser Val Asp Ala Phe Ile Leu Glu Thr Leu Phe Thr Val
        115                 120                 125
Val Asp Ser Phe Ile Pro Ile Ser Arg Gly Ile Thr Lys Lys Arg Asn
    130                 135                 140
Tyr Leu Asp Lys Met Leu Asn Arg Lys Thr Lys Asn Ser Asp Leu Val
145                 150                 155                 160
Ser Leu Ser Tyr Leu Gln Gln Thr Leu Thr Phe Leu Ser Ser Ala Val
                165                 170                 175
Gln Thr Asn Leu Ser Glu Leu Asp Leu Asn Gly Ser Asp Ala Leu Gln
            180                 185                 190
Gln Ile Ile Glu Leu Leu Asn Gln His Pro Leu Asp Xaa Ala Pro Asp
        195                 200                 205
Glu Lys Gly Ala Tyr Ser Asn Ser Asn Tyr Tyr Leu Leu Gly His Ile
    210                 215                 220
Ile Thr Gln Val Ala Asn Met Pro Leu Ser Asp Phe Leu Asn Gln His
225                 230                 235                 240
Phe Phe Glu Pro Leu Ala Met Thr Lys Thr Gln Leu Gly Thr Gln His
                245                 250                 255
Ala Asp Ala Asn Ser Tyr Asp Asp Leu Asp Phe Thr Asn Gly Lys Pro
            260                 265                 270
Val Ala Leu Gly Arg Gly His Tyr Gln Gly Gly Asp Gly Ala Val Val
        275                 280                 285
Ser Ser Leu Ala Asp Leu Ala Ile Trp Ala Arg Ala Val Leu Gln Arg
    290                 295                 300
Arg Ile Leu Pro Glu Ser Ala Trp Asp Glu Ala Leu Thr Leu Thr His
305                 310                 315                 320
Asp Phe Tyr Gly Met Gly Trp Met Lys Ser Arg Thr Gln His Trp Leu
                325                 330                 335
Ser His Asn Gly His Ile Phe Gly Tyr Trp Ala Phe Phe Asp Val Ser
            340                 345                 350
Phe Glu Lys Gln Leu Ala Gln Ile Thr Leu Thr Asn Met Ser Pro Gly
```

```
        355                 360                 365
Val Glu Thr Leu Lys Lys Trp Gln Glu Glu Met Ala Asn Trp Arg Ala
    370                 375                 380
Ser Leu
385

<210> 88
<211> 357
<212> PRT
<213> Lactobacillus rhamnosus

<400> 88
Leu Asp Asn Gln Asp Ala Asp Phe Lys Pro Thr Ile Gln Ile Leu Asp
 1               5                  10                  15
Glu Val Gly Lys Val Val Asn Pro Asp Ile Met Pro Asp Leu Ser Asp
            20                  25                  30
Asp Gln Leu Val Asp Leu Met Ser Lys Met Val Trp Gln Arg Val Leu
        35                  40                  45
Asp Gln Arg Ala Thr Ala Leu Asn Arg Gln Gly Arg Leu Gly Phe Tyr
    50                  55                  60
Ala Pro Ser Ala Gly Glu Glu Ala Ser Met Ile Gly Ser His Ala Ala
65                  70                  75                  80
Met Lys Ser Ser Asp Trp Leu Leu Pro Ala Tyr Arg Asp Leu Pro Gln
                85                  90                  95
Leu Ile Gln His Gly Leu Pro Leu Asp Lys Ala Phe Leu Trp Ser Arg
            100                 105                 110
Gly His Val Ala Gly Asn Glu Tyr Pro Glu Asp Phe His Ala Leu Pro
        115                 120                 125
Pro Gln Ile Ile Ile Gly Ala Gln Tyr Val Gln Thr Ala Gly Val Ala
    130                 135                 140
Leu Gly Leu Lys Lys Asn Gly Ser Asp Glu Val Ala Phe Thr Tyr Thr
145                 150                 155                 160
Gly Asp Gly Gly Thr Ser Gln Gly Asp Phe Tyr Glu Gly Val Asn Phe
                165                 170                 175
Ala Gly His Phe Lys Ala Pro Ala Leu Phe Ile Val Gln Asp Asn Gly
            180                 185                 190
Phe Ala Ile Ser Val Pro Arg Ala Ser Gln Thr Ala Ala Lys Thr Leu
        195                 200                 205
Ala Gln Lys Ala Val Ala Ala Gly Val Pro Gly Val Gln Val Asp Gly
    210                 215                 220
Met Asp Ala Leu Ala Val Tyr Glu Val Thr Lys Glu Ala Arg Ala Trp
225                 230                 235                 240
Ala Ala Ala Gly Asn Gly Pro Val Leu Ile Glu Thr Leu Thr Tyr Arg
                245                 250                 255
Tyr Gly Pro His Thr Leu Ser Gly Asp Asp Pro Thr Arg Tyr Arg Ser
            260                 265                 270
Lys Glu Thr Asp Glu Leu Trp Gln Lys Arg Asp Pro Leu Ile Arg Met
        275                 280                 285
Arg Asn Tyr Leu Thr Asp Lys Gly Leu Trp Ser Lys Asp Lys Glu Asp
    290                 295                 300
Ala Leu Ile Glu Lys Val Lys Asp Glu Ile Lys Asp Ala Ile Asn Lys
305                 310                 315                 320
Ala Asp Lys Ala Pro Gln Gln Thr Val Ser Arg Phe Leu Lys Asp Thr
                325                 330                 335
Tyr Glu Val Ala Pro Gln Asn Val Ala Glu Gln Leu Ala Glu Phe Gln
            340                 345                 350
Gly Lys Glu Ser Lys
```

355

<210> 89
<211> 436
<212> PRT
<213> Lactobacillus rhamnosus

<400> 89
Ser Val Leu Asn Ile Asn Gly Gly Asn Leu Thr Leu Thr Asp Asp Gly
1 5 10 15
Val Ser Ala Gly Thr Leu Thr Gly Gly Gly Phe Leu Asn Ile Ser Gly
20 25 30
Gly Val Leu Asp Ile Thr Gly Gly Asn His Thr Phe Ala Val Ser Thr
35 40 45
Ile Ile Ala Lys Asp Ala Thr Val Arg Met Asn Asp Val Ser Gly Leu
50 55 60
Gly Thr Gly Asn Ile Ser Asn Ala Gly Thr Leu Ser Leu Thr His Ala
65 70 75 80
Ser Gly Leu Leu Ser Asn Asn Leu Ser Gly Ser Gly Thr Val Ser Leu
85 90 95
Ile Asn Ser Asp Thr Gln Ile Ser Gly Asn Asn Ser Asn Tyr Ser Gly
100 105 110
Leu Phe Val Val Asp Thr Ser Ser Gln Leu Thr Ala Thr Gly Ala Gln
115 120 125
Asn Leu Gly Ile Ala Ser Val Ser Asn Arg Gly Ile Leu Gln Leu Asn
130 135 140
Asn Thr Thr Asp Trp Gln Leu Ile Asn Asn Val Thr Gly Thr Gly Asn
145 150 155 160
Val Arg Lys Thr Gly Ser Gly Ser Leu Thr Val Arg Ser Asn Ala Ala
165 170 175
Trp Ser Gly Gln Thr Asp Ile Asp Asp Gly Ser Leu Ile Leu Gly Gln
180 185 190
Ser Asp Ala Pro Val Met Leu Ala Ser Ser Leu Val Asn Ile Ala Lys
195 200 205
Asn Gly Lys Leu Thr Gly Phe Gly Gly Val Val Gly Asn Val Thr Asn
210 215 220
Ser Gly Ser Leu Asp Leu Arg Ser Ala Ala Pro Gly Asn Ile Leu Thr
225 230 235 240
Ile Gly Gly Asn Tyr Thr Gly Asn Asn Gly Thr Leu Leu Ile Asn Thr
245 250 255
Val Leu Asp Asp Ser Ser Ser Ala Thr Asp Lys Leu Val Ile Lys Gly
260 265 270
Asp Ala Ser Gly Lys Thr Arg Val Ala Val Thr Asn Val Gly Gly Ser
275 280 285
Gly Ala Asn Thr Leu Asn Ser Ile Glu Val Ile His Val Asp Gly Asn
290 295 300
Ala Ala Asn Ala Glu Phe Ile Gln Ala Gly Arg Ile Ala Ala Gly Ala
305 310 315 320
Tyr Asp Tyr Thr Leu Gly Arg Gly Pro Gly Ser Asn Tyr Gly Asn Trp
325 330 335
Tyr Leu Ser Ser Ser Lys Asn Thr Pro Glu Pro Arg Pro Asp Pro Glu
340 345 350
Pro Thr Pro Glu Gly His Asp Asn Asn Leu Arg Pro Glu Ala Ser Ser
355 360 365
Tyr Thr Ala Asn Ile Ala Ala Ala Asn Thr Met Phe Val Thr Arg Leu
370 375 380
His Glu Arg Leu Gly Gln Thr Gln Tyr Val Asp Ala Ile Thr Gly Glu

```
385                 390                 395                 400
Pro Lys Ala Thr Ser Met Trp Met Arg His Glu Gly Gly His Asn Arg
                405                 410                 415
Trp Arg Asp Gly Ser Gly Gln Leu Lys Thr Gln Ser Asn Arg Tyr Val
            420                 425                 430
Ile Gln Leu Gly
        435
```

<210> 90
<211> 215
<212> PRT
<213> Lactobacillus rhamnosus

<400> 90

```
Met Lys Ile Leu Ile Thr Gly Ala Gln Gly Gln Leu Gly Thr Glu Leu
 1               5                  10                  15
Arg His Leu Leu Asp Ala Arg Gly Ile Thr Tyr Arg Ala Thr Asp Ala
            20                  25                  30
Lys Asp Leu Asp Ile Thr Asp Glu Ala Ala Val Asn Gln Tyr Phe Ala
        35                  40                  45
Asp Tyr Gln Pro Asp Val Val Tyr His Cys Ala Ala Tyr Thr Ala Val
    50                  55                  60
Asp Lys Ala Glu Asp Glu Ala Lys Ala Leu Asn Gln Leu Val Asn Val
65                  70                  75                  80
Asp Gly Thr Arg Asn Leu Ala Lys Ala Ala Ala Lys Val Asp Ala Thr
                85                  90                  95
Leu Val Tyr Ile Ser Thr Asp Tyr Val Phe Asp Gly Asp Ser Lys Glu
            100                 105                 110
Ile Tyr Thr Val Asp Asp Gln Pro Ala Pro Arg Asn Glu Tyr Gly Arg
        115                 120                 125
Ala Lys Tyr Glu Gly Glu Gln Gln Val Gln Lys Tyr Leu Lys Lys Tyr
    130                 135                 140
Tyr Ile Ile Arg Thr Ser Trp Val Phe Gly Glu Tyr Gly His Asn Phe
145                 150                 155                 160
Val Tyr Thr Met Leu Asn Leu Ala Lys Thr His Lys Glu Leu Thr Val
                165                 170                 175
Val Asp Asp His Gln Glu Ser Phe Ser Val Ser Ser Ser Arg Thr Phe
            180                 185                 190
Val Lys Tyr Gln His Glu His Leu Ile Tyr Ser Arg Pro Val Pro Tyr
        195                 200                 205
Arg Pro His Leu Pro Gly Ile
    210                 215
```

<210> 91
<211> 640
<212> PRT
<213> Lactobacillus rhamnosus

<220>
<221> VARIANT
<222> (1)...(640)
<223> Xaa = Any Amino Acid

<400> 91

```
Met Leu Gly Gly Lys Gln Met Pro Glu Val Lys Lys Phe Glu Ala Gly
 1               5                  10                  15
Thr Tyr Asp Val Ile Val Val Gly Ala Gly His Ala Gly Xaa Val Lys
```

```
            20                  25                  30
Pro Ala Leu Ala Ala Ala Arg Met Gly Glu Lys Thr Leu Leu Leu Thr
        35                  40                  45
Ile Ser Leu Glu Met Leu Ala Phe Met Pro Cys Asn Pro Ser Leu Gly
    50                  55                  60
Gly Pro Ala Lys Gly Ile Val Val Arg Glu Ile Asp Ala Leu Gly Gly
65                  70                  75                  80
Glu Met Gly Lys Asn Ile Asp Arg Thr Tyr Ile Gln Met Arg Met Leu
                85                  90                  95
Asn Thr Gly Lys Gly Pro Ala Val Arg Ala Leu Arg Ala Gln Ala Asp
            100                 105                 110
Lys Ala Ala Tyr His Arg Ser Met Lys His Val Ile Glu Asp Thr Pro
        115                 120                 125
His Leu Asp Leu Arg Gln Gly Leu Ala Thr Glu Val Leu Val Glu Asp
    130                 135                 140
Gly Lys Ala Val Gly Ile Val Ala Ala Thr Gly Ala Ile Tyr Arg Ala
145                 150                 155                 160
Lys Ser Ile Val Leu Thr Ala Gly Thr Ser Ser Arg Gly Lys Ile Ile
                165                 170                 175
Ile Gly Glu Leu Met Tyr Ser Ser Gly Pro Asn Asn Ser Leu Pro Ser
            180                 185                 190
Ile Lys Leu Ser Glu Asn Leu Glu Gln Leu Gly Phe Lys Leu Arg Arg
        195                 200                 205
Phe Lys Thr Gly Thr Pro Pro Arg Val Asn Gly Asn Thr Ile Asp Phe
    210                 215                 220
Ser Lys Thr Glu Glu Gln Pro Gly Asp Lys Thr Pro Asn His Phe Ser
225                 230                 235                 240
Phe Thr Thr Pro Asp Ser Val Tyr Leu Lys Asp Gln Leu Ser Cys Trp
                245                 250                 255
Met Thr Tyr Thr Asn Ala Thr Thr His Gln Ile Ile Arg Glu Asn Leu
            260                 265                 270
Asp Arg Ala Pro Met Phe Ser Gly Val Ile Lys Gly Val Gly Pro Arg
        275                 280                 285
Tyr Cys Pro Ser Ile Glu Asp Lys Ile Val Arg Phe Ala Asp Lys Pro
    290                 295                 300
Arg His Gln Leu Phe Leu Glu Pro Glu Gly Arg Asp Thr Ser Glu Tyr
305                 310                 315                 320
Tyr Val Gly Asp Phe Ser Thr Ser Met Pro Glu Glu Ile Gln Leu Lys
                325                 330                 335
Met Leu His Ser Val Ala Gly Leu Glu His Ala Glu Leu Met Arg Ala
            340                 345                 350
Gly Tyr Ala Ile Glu Tyr Asp Val Ile Glu Pro Trp Gln Leu Lys Ala
        355                 360                 365
Thr Leu Glu Thr Lys Val Val Glu Asn Leu Tyr Thr Ala Gly Gln Met
    370                 375                 380
Asn Gly Thr Ser Gly Tyr Glu Glu Ala Ala Gly Gln Gly Ile Val Ala
385                 390                 395                 400
Gly Ile Asn Ala Ala Arg Arg Ala Gln Gly Lys Gly Pro Phe Thr Leu
                405                 410                 415
Lys Arg Ser Asp Ala Tyr Ile Gly Val Met Ile Asp Asp Leu Val Thr
            420                 425                 430
Lys Gly Thr Asn Glu Pro Tyr Arg Leu Leu Thr Ser Arg Ala Glu Tyr
        435                 440                 445
Arg Leu Leu Leu Arg His Asp Asn Ala Asp Leu Arg Leu Thr Pro Met
    450                 455                 460
Gly His Glu Leu Gly Leu Ile Ser Asp Gln Arg Tyr Ala Val Phe Leu
465                 470                 475                 480
```

```
Ala Lys Arg Gln Ala Ile Thr Asp Glu Leu Ala Arg Leu Glu His Thr
                485                 490                 495
Arg Leu Lys Pro Lys Asp Val Asn Pro Trp Leu Glu Ala His His Phe
            500                 505                 510
Ala Ser Leu Lys Asp Gly Val Leu Ala Ser Asp Phe Leu Lys Arg Pro
        515                 520                 525
Glu Ile Asn Tyr Gln Thr Leu Glu Gln Phe Leu Pro Glu Asn Pro Thr
    530                 535                 540
Leu Asp His Arg Val Ile Glu Gln Val Glu Ile Gln Ile Lys Tyr Ala
545                 550                 555                 560
Gly Tyr Ile Ala Lys Glu Glu Xaa Gln Cys Ala Lys Leu Lys Arg Leu
                565                 570                 575
Glu Gly Lys Lys Ile Pro Ala Arg Ile Asn Tyr Glu Ala Ile Asn Gly
            580                 585                 590
Leu Ala Thr Glu Ala Arg Gln Lys Leu Val Lys Ile Gln Pro Glu Thr
        595                 600                 605
Ile Ala Gln Ala Ser Arg Ile Ser Gly Val Asn Pro Ala Asp Val Ala
    610                 615                 620
Ile Leu Ser Val Tyr Ile Glu Gln Gly Arg Ile Ser Lys Val Ala Gln
625                 630                 635                 640
```

<210> 92
<211> 254
<212> PRT
<213> Lactobacillus rhamnosus

<400> 92

```
Pro Leu Ser Thr Met Met Leu Ala Gly Ile Arg Asp Ile Leu Val Ile
 1               5                  10                  15
Ser Thr Pro Arg Asp Ile Asp Arg Phe Gln Asp Leu Leu Lys Asp Gly
            20                  25                  30
Lys Gln Leu Gly Leu Asn Ile Ser Tyr Lys Ile Gln Glu Lys Pro Asn
        35                  40                  45
Gly Leu Ala Glu Ala Phe Ile Val Gly Ala Asp Phe Ile Gly Asp Asp
    50                  55                  60
Ser Val Cys Leu Ile Leu Gly Asp Asn Ile Phe Tyr Gly Ser Gly Leu
65                  70                  75                  80
Ser Lys Leu Val Gln Arg Ser Ala Ala Lys Thr Thr Gly Ala Thr Val
                85                  90                  95
Phe Gly Tyr Gln Val Asn Asp Pro Glu Arg Phe Gly Val Val Ala Phe
            100                 105                 110
Asp Glu Gln His His Val Gln Ser Ile Val Glu Lys Pro Glu His Pro
        115                 120                 125
Glu Ser Asn Phe Ala Val Thr Gly Met Tyr Phe Tyr Asp Asn Gln Val
    130                 135                 140
Val Asp Ile Ala Lys Asn Leu Lys Pro Ser Pro Arg Gly Glu Leu Glu
145                 150                 155                 160
Ile Thr Asp Val Asn Lys Ala Tyr Leu Glu Arg Gly Gln Leu Asp Val
                165                 170                 175
Glu Leu Leu Gly Arg Gly Phe Ala Trp Leu Asp Thr Gly Thr His Glu
            180                 185                 190
Ser Leu His Glu Ala Ala Ser Phe Ile Glu Thr Val Gln Lys Arg Gln
        195                 200                 205
Asn Leu Lys Ile Ala Cys Leu Glu Glu Val Ala Tyr Arg Met Gly Tyr
    210                 215                 220
Ile Asp Arg Asp Gln Leu Arg Lys Leu Ala Gln Pro Leu Lys Lys Asn
225                 230                 235                 240
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Asp Tyr Gly Gln Tyr Ile Leu Arg Leu Ala Asp Glu Glu Asp
                245                 250

<210> 93
<211> 312
<212> PRT
<213> Lactobacillus rhamnosus

<400> 93
Met Ala Ile Asn Leu Val Gly Ile Asn Asp Ala Asn Leu Thr Leu Ile
 1               5                  10                  15
Glu Glu Gly Leu Asn Val Arg Ile Ser Pro Phe Gly Asp Glu Leu Arg
            20                  25                  30
Ile Ser Gly Glu Thr Glu Ala Val Ser Leu Thr Leu Gln Leu Leu Glu
        35                  40                  45
Ala Ala Thr Lys Leu Leu Ala Gln Gly Ile Lys Leu Ser Pro Gln Asp
    50                  55                  60
Ile Ala Ser Ala Val Ala Met Ala Lys Arg Gly Thr Leu Glu Tyr Phe
65                  70                  75                  80
Ala Asp Met Tyr Ser Glu Thr Leu Leu Arg Asp Ala Lys Gly Gln Pro
                85                  90                  95
Ile Arg Ile Lys Asn Phe Gly Gln Arg Gln Tyr Val Asp Ala Ile Lys
            100                 105                 110
His Asn Asp Ile Thr Phe Gly Ile Gly Pro Ala Gly Thr Gly Lys Thr
        115                 120                 125
Phe Leu Ala Val Val Met Ala Val Ala Ala Met Lys Ala Gly Gln Val
    130                 135                 140
Glu Arg Ile Ile Leu Thr Arg Pro Ala Val Glu Ala Gly Glu Ser Leu
145                 150                 155                 160
Gly Phe Leu Pro Gly Asp Leu Lys Glu Lys Val Asp Pro Tyr Leu Arg
                165                 170                 175
Pro Val Tyr Asp Ala Leu Tyr Ala Val Leu Gly Lys Glu His Thr Asp
            180                 185                 190
Arg Leu Met Asp Arg Gly Val Ile Glu Ile Ala Pro Leu Ala Tyr Met
        195                 200                 205
Arg Gly Arg Thr Leu Asp Asn Ala Phe Ala Ile Leu Asp Glu Ala Gln
    210                 215                 220
Asn Thr Thr Gln Ala Gln Met Lys Met Phe Leu Thr Arg Leu Gly Phe
225                 230                 235                 240
Gly Ser Lys Met Ile Val Asn Gly Asp Val Thr Gln Ile Asp Leu Pro
                245                 250                 255
His Asn Ala Lys Ser Gly Leu Leu Gln Ala Glu Gln Leu Leu Lys Gly
            260                 265                 270
Ile Ser His Ile Ala Phe Thr Gln Phe Ser Ala Gln Asp Val Val Arg
        275                 280                 285
His Pro Val Val Ala Lys Ile Ile Glu Ala Tyr Gly Lys His Asp Leu
    290                 295                 300
Gln Leu Gln Lys Gln Thr Lys Glu
305                 310

<210> 94
<211> 280
<212> PRT
<213> Lactobacillus rhamnosus

<400> 94
Met Lys Lys Phe Asp Lys Met Met Asp Trp Leu Ala Asp Val Tyr Val
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            20                  25                  30
Ala Ala Gln Leu Ala Leu Lys Asp Thr Arg Leu Asn Arg Thr Phe Ala
        35                  40                  45
Thr Gly Ile Ser Gly Leu Ser His Ala Val Asp Ser Ile Ser Ala Ile
    50                  55                  60
Lys Tyr Gly His Val Lys Ala Ile Arg Asp Glu Asn Gly Val Ala Ile
65                  70                  75                  80
Asp Phe Val Ala Asp Asn Asp Asp Tyr Pro Arg Tyr Gly Asn Asn Asp
                85                  90                  95
Asp Arg Ala Asp Asn Ile Ala Lys Trp Leu Val Lys Thr Phe Tyr Asn
            100                 105                 110
Lys Met Asn Thr His His Leu Tyr Arg Gly Ala Lys Leu Ser Thr Ser
        115                 120                 125
Val Leu Thr Ile Thr Ser Asn Val Val Tyr Gly Lys Asn Thr Gly Thr
    130                 135                 140
Thr Pro Asn Gly Arg Gln Lys Gly Glu Pro Phe Ser Pro Gly Ala Asn
145                 150                 155                 160
Pro Ala Tyr Gly Ala Glu Lys Asn Gly Ala Leu Ala Ser Leu Met Ser
                165                 170                 175
Thr Ala Lys Ile Pro Tyr His Tyr Ala Thr Asp Gly Ile Ser Asn Thr
            180                 185                 190
Phe Gly Val Thr Pro Asn Thr Leu Gly His Asp Asp Glu Thr Arg Lys
        195                 200                 205
Asp Thr Leu Val His Met Val Asp Gly Tyr Met Glu Asn Ser Gly Met
    210                 215                 220
His Leu Asn Ile Asn Val Phe Asn Lys Glu Thr Leu Ile Asp Ala Gln
225                 230                 235                 240
Lys His Pro Glu Glu Tyr Pro Thr Leu Thr Val Arg Val Ser Gly Tyr
                245                 250                 255
Cys Val Tyr Phe Ala Asp Leu Thr Lys Glu Gln Gln Asp Asp Val Ile
            260                 265                 270
Ala Arg Thr Phe Phe Asp Glu Met
        275                 280
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<210> 95
<211> 447
<212> PRT
<213> Lactobacillus rhamnosus

<400> 95

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 1               5                  10                  15
Gln Thr Glu Leu Asp Leu Leu Ile Val Gly Gly Gly Ile Thr Gly Ala
            20                  25                  30
Gly Val Ala Ile Gln Ala Ala Ala Ser Gly Leu Lys Thr Gly Leu Ile
        35                  40                  45
Glu Met Gln Asp Phe Ala Glu Gly Thr Ser Ser Arg Ser Thr Lys Leu
    50                  55                  60
Val His Gly Gly Ile Arg Tyr Leu Lys Thr Phe Asp Val Gly Val Val
65                  70                  75                  80
Ala Asp Thr Val Lys Glu Arg Ala Val Val Gln Gly Ile Ala Pro His
                85                  90                  95
Ile Pro Arg Pro Phe Pro Met Leu Leu Pro Ile Tyr Gln Glu Ala Gly
            100                 105                 110
Ser Thr Phe Asp Met Phe Ser Ile Lys Ile Ala Met Asp Leu Tyr Asp
```

```
        115                 120                 125
Arg Leu Ala Asn Val Glu Gly Ser Gln Tyr Ala Asn Tyr Thr Val Thr
    130                 135                 140
Lys Asp Glu Ile Leu Gln Arg Glu Pro His Leu Ala Ser Asp Gly Leu
145                 150                 155                 160
Gln Gly Gly Gly Val Tyr Leu Asp Phe Val Asn Asn Asp Ala Arg Leu
                165                 170                 175
Val Ile Glu Asn Ile Lys Glu Ala Ala Glu Leu Gly Gly Leu Met Ala
            180                 185                 190
Ser Arg Val Gln Ala Ile Gly Val Leu His Asp Asp Ala Gly Gln Val
        195                 200                 205
Asn Gly Leu Gln Val Lys Asp Leu Leu Asp Gly Ser Val Phe Asp Ile
    210                 215                 220
His Ala Lys Leu Val Ile Asn Thr Thr Gly Pro Trp Ser Asp Lys Phe
225                 230                 235                 240
Lys Ala Leu Asp Gln Ala Glu Asp Gln Thr Pro Thr Leu Arg Pro Thr
                245                 250                 255
Lys Gly Val His Leu Val Val Asp Gly Ser Arg Leu Pro Val Pro Gln
            260                 265                 270
Pro Thr Tyr Met Asp Thr Gly Leu Asn Asp Gly Arg Met Phe Phe Val
        275                 280                 285
Val Pro Arg Glu Gly Lys Thr Tyr Phe Gly Thr Thr Asp Thr Asp Tyr
    290                 295                 300
His Gly Asp Phe Asn His Pro Gln Val Glu Gln Ala Asp Val Asp Tyr
305                 310                 315                 320
Leu Leu Lys Val Ile Asn Lys Arg Tyr Pro Gln Ser His Ile Thr Leu
                325                 330                 335
Asp Asp Ile Glu Ala Ser Trp Ala Gly Leu Arg Pro Leu Ile Ala Asn
            340                 345                 350
Asn Gly Ser Ser Asp Tyr Asn Gly Gly Gly Ala Asn Thr Gly Lys Val
        355                 360                 365
Ser Asp Asp Ser Phe Glu Ala Leu Ile Arg Val Val Asp Asp Tyr Glu
    370                 375                 380
Asp Asn Gln Ala Thr Arg Ala Asp Val Glu His Ala Ile Ser Lys Leu
385                 390                 395                 400
Glu Thr Ala His Ala Glu Ala Ala Leu Ser Pro Ser Gln Val Ser Arg
                405                 410                 415
Gly Ser Ser Leu Arg Gln Ala Asp Asp Gly Met Ile Thr Leu Ser Gly
            420                 425                 430
Gly Lys Ile Thr Asp Tyr Arg Lys Met Ala Ala Gly Ala Leu Ala
        435                 440                 445
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<210> 96
<211> 242
<212> PRT
<213> Lactobacillus rhamnosus

<400> 96

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Asp Leu Phe Cys Pro Asp Ile Thr Ala Asp Ile Leu Thr Arg Lys Asp
 1               5                  10                  15
Asp Leu Gly Ser Asp Lys Pro Ile Val Asp Val Ile Leu Asp Arg Ala
            20                  25                  30
Gly Asn Lys Gly Thr Gly Lys Trp Ser Ser Gln Ser Ala Leu Glu Leu
        35                  40                  45
Gly Val Pro Gln Ser Val Ile Thr Glu Ser Val Tyr Ala Arg Tyr Ile
    50                  55                  60
Ser Ala Met Lys Gln Glu Arg Val Ala Ala Ser Lys Val Leu Pro Lys
```

```
65                  70                  75                  80
Pro Val Gly Asn Val Thr Ile Asp Lys Lys Glu Ala Ile Glu Met Ile
                85                  90                  95
Arg Lys Ala Leu Tyr Phe Ser Lys Leu Met Ser Tyr Ala Gln Gly Phe
            100                 105                 110
Glu Gln Met Arg Val Ala Ser Asp Asn Tyr Asp Trp Asn Leu Gln Tyr
        115                 120                 125
Gly Glu Leu Ala Lys Ile Trp Arg Ala Gly Cys Ile Ile Arg Ala Arg
    130                 135                 140
Phe Leu Gln Asn Ile Thr Asp Ala Tyr Asp Lys Lys Pro Asp Leu Gln
145                 150                 155                 160
Asn Leu Leu Leu Asp Asp Tyr Phe Leu Asn Ile Ala Lys Asn Tyr Gln
                165                 170                 175
Glu Ser Val Arg Asp Leu Val Gly Leu Ala Val Lys Ala Gly Val Pro
            180                 185                 190
Val Pro Gly Phe Ser Ala Ala Ile Ser Tyr Tyr Asp Ser Tyr Arg Ala
        195                 200                 205
Pro Val Leu Pro Ala Asn Leu Thr Gln Ala Gln Arg Asp Tyr Phe Gly
    210                 215                 220
Ala His Thr Tyr Glu Arg Thr Asp Arg Asp Gly Ile Phe His Tyr Thr
225                 230                 235                 240
Trp Tyr
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<210> 97
<211> 323
<212> PRT
<213> Lactobacillus rhamnosus

<400> 97

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Glu Asp Phe Phe Ile Gln Ile Ser Ala Thr Gln His His Ile Pro Asp
 1               5                  10                  15
Cys Cys Asp Gln Ile Pro Thr Gly Asp Phe Ser Phe Phe Asp Asn Thr
            20                  25                  30
Leu Asp Val Ala Asn Leu Leu Asn Ile Val Pro Lys Arg Tyr Gln Asp
        35                  40                  45
Leu Asn Leu Ser Pro Leu Asp Thr Tyr Phe Ala Gln Ala Arg Gly Tyr
    50                  55                  60
Gln Gly Glu Ala Gly Asp Val Lys Ala Leu Ala Met Lys Lys Trp Phe
65                  70                  75                  80
Asn Thr Asn Tyr His Tyr Leu Val Pro Glu Phe Asp Arg Asp Thr Lys
                85                  90                  95
Ile Gln Val Thr Asp Trp Gln Leu Phe Val Gln Phe Glu Glu Ala Lys
            100                 105                 110
Ala Leu Gly Ile Asn Gly Arg Pro Thr Leu Ile Gly Pro Tyr Thr Leu
        115                 120                 125
Leu Lys Leu Ser Arg Phe Ile Asp Val Val Pro Asp Asp Phe Val Ala
    130                 135                 140
Asp Leu Ile Ser Ala Tyr Thr Thr Ile Ile Asp Arg Leu His Asp Ala
145                 150                 155                 160
Gly Ala Asp Trp Val Gln Leu Asp Glu Pro Ala Leu Val Tyr Asp Gln
                165                 170                 175
Thr Asp Ala Asp Leu Ala Leu Phe Glu Arg Leu Tyr Thr Pro Ile Leu
            180                 185                 190
Thr Gln Lys Lys Ala Ala Lys Ile Leu Val Gln Thr Tyr Phe Gly Asp
        195                 200                 205
Leu Thr Asp Ser Phe Asp Arg Ile Gln Lys Leu Pro Phe Asp Gly Phe
```

```
    210                 215                 220
Gly Leu Asp Phe Val Glu Gly Tyr Ala Asn Leu Asp Leu Leu Lys Gln
225                 230                 235                 240
His Gly Phe Pro Ala His Ala Thr Leu Phe Ala Gly Ile Val Asn Gly
                245                 250                 255
Lys Asn Ile Trp Arg Thr His Tyr Ala Asp Ala Leu Ala Thr Ile Lys
            260                 265                 270
Gln Leu Ala Thr Ile Thr Asp Lys Leu Val Leu Ser Thr Ser Thr Ser
        275                 280                 285
Leu Leu His Val Pro Tyr Thr Leu Arg Asn Glu Thr His Leu Lys Pro
    290                 295                 300
Glu Glu Lys Gln Tyr Leu Ala Phe Ala Glu Glu Lys Leu Asn Glu Leu
305                 310                 315                 320
His Glu Leu
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<210> 98
<211> 296
<212> PRT
<213> Lactobacillus rhamnosus

<400> 98

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Gly Pro Ala Ile Phe Gly Phe Ile Pro Met Gln Asp Gly Ser Pro Ala
 1               5                  10                  15
Pro Gly Leu Ser Asn Ile Thr Ala Glu Gly Trp Phe Pro His Gly Gly
            20                  25                  30
Leu Pro Ile Leu Met Thr Met Val Ala Val Asn Phe Ala Phe Ser Gly
        35                  40                  45
Thr Glu Leu Ile Gly Ile Ala Ala Gly Glu Thr Glu Asn Pro Arg Lys
    50                  55                  60
Val Ile Pro Val Ala Ile Arg Thr Thr Ile Ala Arg Leu Ile Ile Phe
65                  70                  75                  80
Phe Ile Gly Thr Val Phe Val Leu Ala Ala Leu Ile Pro Met Gln Gln
                85                  90                  95
Val Gly Val Glu Lys Ser Pro Phe Val Leu Val Phe Glu Lys Val Gly
            100                 105                 110
Ile Pro Tyr Ala Ala Asp Ile Phe Asn Phe Val Ile Leu Thr Ala Ile
        115                 120                 125
Leu Cys Ala Ala Asn Ser Gly Leu Tyr Ala Ser Gly Arg Met Leu Trp
    130                 135                 140
Ser Leu Ser Asn Glu Arg Thr Leu Pro Ala Cys Phe Ala Arg Val Thr
145                 150                 155                 160
Lys Asn Gly Val Pro Leu Thr Ala Leu Ser Val Ser Met Leu Gly Gly
                165                 170                 175
Val Leu Ala Leu Phe Ser Ser Val Val Ala Pro Asn Thr Val Phe Val
            180                 185                 190
Ala Leu Ser Ala Ile Ser Gly Phe Ala Val Val Ala Val Trp Leu Ser
        195                 200                 205
Ile Cys Ala Ser His Phe Val Phe Arg Arg Arg His Leu Gln Gln Gly
    210                 215                 220
Lys Ala Leu Ser Glu Leu His Tyr Arg Ala Pro Trp Tyr Pro Leu Val
225                 230                 235                 240
Pro Val Leu Gly Phe Val Leu Cys Leu Val Ala Cys Val Gly Leu Ala
                245                 250                 255
Phe Asp Pro Ala Gln Arg Ile Ala Leu Trp Cys Gly Leu Pro Phe Val
            260                 265                 270
Ala Leu Cys Tyr Gly Ala Tyr Phe Leu Thr Gln Pro Arg Asn Ala Lys
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        275                 280                 285
Gln Glu Pro Glu His Val Ala Glu
    290                 295

<210> 99
<211> 474
<212> PRT
<213> Lactobacillus rhamnosus

<400> 99
Met Arg Lys Gln Leu Pro Lys Asp Phe Val Ile Gly Gly Ala Thr Ala
 1               5                  10                  15
Ala Tyr Gln Val Glu Gly Ala Thr Lys Glu Asp Gly Lys Gly Arg Val
            20                  25                  30
Leu Trp Asp Asp Phe Leu Glu Lys Gln Gly Arg Phe Ser Pro Asp Pro
        35                  40                  45
Ala Ala Asp Phe Tyr His Arg Tyr Asp Glu Asp Leu Ala Leu Ala Glu
    50                  55                  60
Ala Tyr Gly His Gln Val Ile Arg Leu Ser Ile Ala Trp Ser Arg Ile
65                  70                  75                  80
Phe Ser Asp Gly Ala Gly Ala Val Glu Ser Arg Gly Val Ala Phe Tyr
                85                  90                  95
His Arg Leu Phe Ala Ala Cys Ala Lys His His Leu Ile Pro Phe Val
            100                 105                 110
Thr Leu His His Phe Asp Thr Pro Glu Arg Leu His Glu Ile Gly Asp
        115                 120                 125
Trp Leu Ser Gln Glu Met Leu Glu Asp Phe Val Glu Tyr Ala Arg Phe
    130                 135                 140
Cys Phe Glu Glu Phe Pro Glu Ile Lys His Trp Ile Thr Ile Asn Glu
145                 150                 155                 160
Pro Thr Ser Met Ala Val Gln Gln Tyr Thr Ser Gly Thr Phe Pro Pro
                165                 170                 175
Ala Glu Thr Gly His Phe Asp Lys Thr Phe Gln Ala Glu His Asn Gln
            180                 185                 190
Ile Val Ala His Ala Arg Ile Val Asn Leu Tyr Lys Ser Met Gly Leu
        195                 200                 205
Asp Gly Glu Ile Gly Ile Val His Ala Leu Gln Thr Pro Tyr Pro Tyr
    210                 215                 220
Ser Asp Ser Ser Glu Asp Gln His Ala Ala Asp Leu Gln Asp Ala Leu
225                 230                 235                 240
Glu Asn Arg Leu Tyr Leu Asp Gly Thr Leu Ala Gly Asp Tyr Ala Pro
                245                 250                 255
Lys Thr Leu Ala Leu Ile Lys Glu Ile Leu Ala Ala Asn Gln Gln Pro
            260                 265                 270
Met Phe Lys Tyr Thr Asp Glu Glu Met Ala Ala Ile Lys Lys Ala Ala
        275                 280                 285
His Gln Leu Asp Phe Val Gly Val Asn Asn Tyr Phe Ser Lys Trp Leu
    290                 295                 300
Arg Ala Tyr His Gly Lys Ser Glu Thr Ile His Asn Gly Asp Gly Ser
305                 310                 315                 320
Lys Gly Ser Ser Val Ala Arg Leu His Gly Ile Gly Glu Glu Lys Lys
                325                 330                 335
Pro Ala Gly Ile Glu Thr Thr Asp Trp Asp Trp Ser Ile Tyr Pro Arg
            340                 345                 350
Gly Met Tyr Asp Met Leu Met Arg Ile His Gln Asp Tyr Pro Leu Val
        355                 360                 365
Pro Ala Ile Tyr Val Thr Glu Asn Gly Ile Gly Leu Lys Glu Ser Leu
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    370                 375                 380
Pro Ala Glu Val Thr Pro Asn Thr Val Ile Ala Asp Pro Lys Arg Ile
385                 390                 395                 400
Asp Tyr Leu Lys Lys Tyr Leu Ser Ala Ile Ala Asp Ala Ile Gln Ala
                405                 410                 415
Gly Ala Asn Val Lys Gly Tyr Phe Val Trp Ser Leu Gln Asp Gln Phe
            420                 425                 430
Ser Trp Thr Asn Gly Tyr Ser Lys Arg Tyr Gly Leu Phe Phe Val Asp
        435                 440                 445
Phe Pro Thr Gln Lys Arg Tyr Val Lys Gln Ser Ala Glu Trp Leu Lys
    450                 455                 460
Gln Val Ser Gln Thr His Val Ile Pro Glu
465                 470

<210> 100
<211> 258
<212> PRT
<213> Lactobacillus rhamnosus

<400> 100
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Ser Ala Gln Pro Asp Val Val Lys Glu Glu Ile Glu Glu Met Ile Gly
            20                  25                  30
Leu Asp Ala Ser Asp Ala Ile Leu Ala Ser Gly Lys Thr Gly Leu Gly
        35                  40                  45
Val Pro Glu Ile Leu Glu Arg Ile Val Ser Asp Ile Pro Ala Pro Ser
    50                  55                  60
Gly Asp Val Asn Ala Pro Leu Gln Ala Leu Ile Phe Asp Ser Val Tyr
65                  70                  75                  80
Asp Asp Tyr Arg Gly Val Val Leu Asp Val Arg Val Lys Glu Gly Gln
                85                  90                  95
Val Lys Val Gly Asp Thr Ile Gln Leu Met Ser Asn Gly Lys Gln Phe
            100                 105                 110
Gln Val Thr Glu Val Gly Val Met Ser Pro Lys Ala Val Lys Arg Asp
        115                 120                 125
Phe Leu Met Val Gly Asp Val Gly Tyr Ile Thr Ala Ser Ile Lys Thr
    130                 135                 140
Ile Gln Asp Thr Arg Val Gly Asp Thr Val Thr Leu Ala Asp Arg Pro
145                 150                 155                 160
Ala Ala Ala Pro Leu Lys Gly Tyr Arg Lys Ile Thr Pro Met Val Tyr
                165                 170                 175
Ser Gly Leu Phe Pro Val Asp Asn Ala Lys Phe Asn Asp Leu Arg Glu
            180                 185                 190
Ala Leu Glu Lys Leu Gln Leu Asn Asp Ala Ala Leu Glu Phe Glu Pro
        195                 200                 205
Glu Thr Ser Gln Ala Leu Gly Phe Gly Phe Arg Cys Gly Phe Leu Gly
    210                 215                 220
Leu Leu His Met Asp Val Val Gln Glu Arg Leu Glu Arg Asp Tyr Gly
225                 230                 235                 240
Leu Asp Leu Ile Met Thr Ala Pro Ser Val Asp Tyr Gln Val Ala Leu
                245                 250                 255
Thr Asp

<210> 101
<211> 418
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<212> PRT
<213> Lactobacillus rhamnosus

<400> 101
Met Asp Val Thr Thr Ile Asp Leu Glu Gln Met Gly Arg Ala Ala Lys
1 5 10 15
Ala Ala Ala Thr Val Leu Ser Gln Leu Thr Thr Ala Gln Lys Asn Ala
20 25 30
Gly Leu Leu Ala Met Val Thr Ala Leu Glu Thr His Thr Glu Thr Ile
35 40 45
Leu Gly Ala Asn His Glu Asp Leu Lys Ala Ala Ala Ser Leu Pro Ala
50 55 60
Lys Phe Thr Asp Arg Leu Val Leu Thr Ala Glu Arg Ile Ala Asp Met
65 70 75 80
Ala Ala Gly Val Arg Gln Val Ala Ala Leu Pro Asp Pro Thr Ala Gln
85 90 95
Thr Asp Lys Ala Trp Val Asn His Ala Gly Leu Asn Ile Ala Gln Lys
100 105 110
Arg Val Pro Leu Gly Val Val Gly Met Ile Tyr Glu Ala Arg Pro Asn
115 120 125
Val Thr Val Asp Ala Ala Ala Leu Thr Phe Lys Ser Gly Asn Ala Val
130 135 140
Ile Leu Arg Gly Gly Lys Glu Ala Leu His Ser Asn Leu Ala Leu Ala
145 150 155 160
Thr Val Leu Gln Ala Ala Leu Thr Ala Gln Gly Leu Pro Lys Asp Ala
165 170 175
Ile Gln Leu Ile Thr Asp Pro Lys Arg Glu Val Ala Asn Gln Met Met
180 185 190
His Leu Asn Gly Tyr Ile Asp Val Leu Ile Pro Arg Gly Gly Arg Gly
195 200 205
Leu Ile Lys Ala Val Val Glu Gln Ala Thr Val Pro Val Ile Glu Thr
210 215 220
Gly Ala Gly Asn Cys His Ile Tyr Val Asp Ala Tyr Ala Gln Ala Gln
225 230 235 240
Met Ala Ile Asp Ile Val Val Asn Ala Lys Val Gln Arg Pro Ser Val
245 250 255
Cys Asn Ala Ala Glu Lys Leu Leu Ile His Ala Asp Val Ala Asn Ala
260 265 270
Gln Leu Pro Leu Ile Ala Ala Ala Leu Gln Ala His Gly Val Glu Leu
275 280 285
Arg Gly Asp Glu Arg Ala Arg Ala Ile Val Pro Asn Met Gln Ile Ala
290 295 300
Thr Glu Glu Asp Trp Asp Thr Glu Tyr Asn Asp Leu Ile Met Ala Val
305 310 315 320
Lys Val Val Asp Ser Glu Glu Glu Ala Ile Ala His Ile Asn Ala His
325 330 335
Asn Thr Lys His Ser Glu Ala Ile Ile Thr Asp Asn Tyr Gln Asn Ser
340 345 350
Gln Gln Phe Leu Gln Gln Val Asp Ala Ala Val Val Tyr Val Asn Ala
355 360 365
Ser Thr Arg Phe Thr Asp Gly Phe Glu Phe Gly Phe Gly Ala Glu Ile
370 375 380
Gly Ile Ser Thr Gln Lys Leu His Ala Arg Gly Pro Met Gly Leu Ala
385 390 395 400
Ala Leu Thr Thr Ile Lys Tyr Gln Val Leu Gly Asn Gly Gln Val Arg
405 410 415
Glu Gly

INTERNATIONAL SEARCH REPORT

International application No.
PCT/NZ01/00286

A. CLASSIFICATION OF SUBJECT MATTER

Int. Cl. [7]: (C12N 15/31, C12R 1:225)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
SEE ELECTRONIC DATA BASES

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
SEE ELECTRONIC DATA BASES

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
SwissProt, PIR, GenPept, embl, GenBank: Sequence IDs 41 - 59, 62 - 101

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
PX	WO 02/12506 A (GENESIS RESEARCH AND DEVELOPMENT CORPORATION LIMITED) 14 February 2002 Sequence ID 50 (equivalent to current Seq ID 64) Sequence ID 47 (equivalent to current Seq ID 69)	3, 5, 11
X	A Holck & H Naes *Journal of General Microbiology* (1992) 138(7) pp 1353-64 "Cloning, sequencing and expression of the gene encoding the cell-envelope-associated proteinase from *Lactobacillus paracasei* subsp. paracasei NCDO 151" & Swiss-Prot Accession Number Q02470 15 July 1998 & GenBank Accession Number M83946 26 April 1993 Whole Document (equivalent to Seq ID 73)	3, 5, 11

[X] Further documents are listed in the continuation of Box C [X] See patent family annex

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
19 March 2002	11 APR 2002
Name and mailing address of the ISA/AU AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA E-mail address: pct@ipaustralia.gov.au Facsimile No. (02) 6285 3929	Authorized officer **CRAIG ALLATT** Telephone No : (02) 6283 2414

INTERNATIONAL SEARCH REPORT

International application No.
PCT/NZ01/00286

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0307011 A (NEDERLANDS INSTITUUT VOOR ZUIVELONDERZOEK) 15 March 1989 & GenPept Accession Number CAA01252 17 February 1994 & GenBank Accession Number A15841 17 February 1994 & Trembl Accession Number E973430 1 November 1998 Whole Document (equivalent to Seq ID 73)	3, 5, 11
X	M. Kiwaki et al *Molecular Microbiology* (1989) 3(3) pp 359 - 369 "Molecular characterization of a cell wall-associated proteinase gene from Streptococcus lactis NCDO763" & GenBank Accession Number X14130 10 February 1999 & GenPept Accession Number CAA32350 10 February 1999 Whole Document (equivalent to Seq ID 73)	3, 5, 11
X	Dossonnet V et al *Journal of Bacteriology* (2000) 182(9) pp 2582 - 90 "Phosphorylation of HPr by the bifunctional HPr Kinase/P-ser-HPr phosphatase from Lactobacillus casei controls catabolite repression and inducer exclusion but not inducer expulsion." & GenBank Accession Number Y18948 25 April 2000 & GenPept Accession Number CAB65151 25 April 2000 Whole Document (equivalent to Seq ID 84)	3, 5, 11
X	K Makino et al *Genes & Genetic Systems* (1999) 74(5) pp 227 - 39 "Complete nucleotide sequence of the prophage VT2-Sakai carrying the verotoxin 2 genes of the enterohemorrhagic Escherichia coli O157:H7 derived from the Sakai outbreak." & GenPept Accession Number BAB33792 7 March 2001 Whole Document	3, 5, 11
X	D. O'Sullivan et al *Molecular Microbiology* (2000) 36(4) pp 866 - 75 "Novel type I restriction specificities through domain shuffling of HsdS subunits in lactococcus lactis" & GenPept Accession Number AAF17616 14 June 2000 Whole Document (equivalent to Seq ID 87)	3, 5, 11
X	R. van Kranenburg & W. M. de Vos *Journal of Bacteriology* (1998) 180(20) pp 5285 - 90 "Characterization of multiple regions involved in replication and mobilization of plasmid pNZ4000 coding for exopolysaccharide production in Lactococcus lactis" & GenBank Accession Number AF036486 17 October 1998 Whole Document (equivalent to Seq ID 87)	3, 5, 11
X	R. van Kranenburg et al *Journal of Bacteriology* (1999) 181(1) pp 338 - 40 "Exopolysaccharide biosynthesis in Lactococcus lactis NIZO B40: functional analysis of the glycosyltransferase genes involved in synthesis of the polysaccharide backbone." & GenPept Accession Number AAD40365 28 June 1999 Whole Document (equivalent to Seq ID 87)	3, 5, 11

INTERNATIONAL SEARCH REPORT

International application No.
PCT/NZ01/00286

C (Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	L. S. Frost et al *Microbiological Reviews* (1994) 58(2) pp 162 - 210 "Analysis of the Sequence and gene products of the transfer region of the F sex factor" & GenPept Accession Number BAA97898 4 July 2000 & GenBank Accession Number AP001918 4 July 2000 Whole Document (equivalent to Seq ID 89)	3, 5, 11
X	F. R. Blattner et al *Science* (1997) 277(5331) pp 1453 - 74 "The complete genome sequence of Escherichia coli K-12. " & EMBL Accession Number AE00134 29 January 1997 & Swiss-Prot Accession Number Q47689 30 May 2000 Whole Document (equivalent to Seq ID 98)	3, 5, 11
X	GenPept Accession Number BAA77928 28 May 1999 "Amino acid permease RocE [Escherichia coli]" Whole Document (equivalent to Seq ID 98)	3, 5, 11
X	Swiss-Prot Accession Number Q47689 30 May 2000 "Probable S-methylmethionine permease" Whole Document (equivalent to Seq ID 98)	3, 5, 11
X	M. J. Gosalbes et al *FEMS Microbiology Letters* (1997) 148(1) pp 83 - 9 "Establishing a model to study the regulation of the lactose operon in Lactobacillus casei." & Swiss-Prot Accession Number P14696 7 April 1997 & GenBank Accession Number Z80834 7 April 1997 Whole Document (equivalent to Seq ID 99)	3, 5, 11
X	E. V. Porter & B. M. Chassy *Gene* (1988) 62(2) pp 263 - 76 "Nucleotide sequence of the beta-D-phosphogalactoside galactohydrolase gene of Lactobacillus casei: comparison to analogous pbg genes of other gram-positive organisms." & GenBank Accession Number M20151 14 February 1996 Whole Document (equivalent to Seq ID 99)	3, 5, 11
X	J. Andrews et al *Gene* (1985) 35(1-2) p 217 - 22 "Nucleotide sequence of the dihydrofolate reductase gene of methotrexate-resistant *Lactobacillus casei*" & GenPept Accession Number AAA25237 26 April 1993 & GenBank Accession Number M10922 26 April 1993 Whole Document (equivalent to Seq IDS 41 & 102)	3, 5, 11
X	S. F. Kim et al *Applied and Environmental Microbiology* (1991) 57(8) pp 2413 - 7. "Cloning and nucleotide sequence of the Lactobacillus casei lactate dehydrogenase gene." & GenPept Accession Number AAA25245 15 March 2000 & GenBank Accession Number M76708 15 March 2000 Whole Document (equivalent to Seq IDS 42 & 103)	3, 5, 11

INTERNATIONAL SEARCH REPORT

International application No.
PCT/NZ01/00286

C (Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	G. Schmidt *Systematic and Applied Microbiology* (1999) 22(3) pp 321 - 8 "Molecular characterisation of the dnaK operon of Lactobacillus sakei LTH681." & GenPept Accession Number CAA06939 15 November 1999 & EMBL Accession Number AJ006274 15 November 1999 Whole Document (equivalent to Seq IDS 43 & 104)	3, 5, 11
X	A. H. F. Griffiths et al "Functional Genomics" in *Modern Genetic Analysis* (1999) (W. H. Freeman & Company: New York) ISBN 0 7167 3597 0 pages 399 - 405 Whole Document	3, 5, 11

INTERNATIONAL SEARCH REPORT

International application No.
PCT/NZ01/00286

Box I **Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos :

because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos : **1, 2, 3 (in part), 4, 5 (in part), 6 - 10, 11 (in part), 12 - 29**

because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

See Supplemental Box

3. ☐ Claims Nos :

because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a)

Box II **Observations where unity of invention is lacking (Continuation of item 3 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

See Supplemental Box

1. ☒ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☒ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/NZ01/00286

Supplemental Box
(To be used when the space in any of Boxes I to VIII is not sufficient)

Continuation of Box No: I

Claims 1, 2, 3 (in part), 4, 5 (in part), 6 - 10, 11 (in part), 12 - 29 are not limited to the technical features that define the inventions. The inventions are the sequences identified in Table 1 pages 14 - 21 and sequences down to 75% smilarity. The claims have not been searched to the extent they encompass material beyond this.

Additionally, due to the complexity of the claims and large number of possibilites, it is not economic to search the full scope of the claims. The search has been limited to Sequence IDs 41 - 59, 62 - 101.

Continuation of Box No: II

You have claimed more than one invention. Rule 13.1 of the PCT states the principle that an International Application should relate to only one invention, or if there is more than one invention, that the inclusion of these inventions in one international application is only permitted if all inventions are so linked as to form a single general inventive concept.

Rule 13.2 of the PCT defines the method for determining whether the requirement of unity of invention is satisfied in respect of a group of inventions claimed in an international application. Unity of invention exists only when there is a technical relationship among the claimed inventions involving one or more of the same or corresponding "special technical features". The expression "special technical features" is defined in Rule 13.2 as meaning those technical features that define a contribution, which each of the inventions, considered as a whole, make over the prior art. The determination is made on the contents of the claims as interpreted in light of the description and drawings (if any).

In the present application, the feature that all sequences come from *Lactobacillus rhamnosus* strain HN001 does not provide a special technical feature. Genes and their expressed proteins from *Lactobacillus rhamnosus* are known (see for example GenBank Accession number AF261767). The applicant has provided no evidence that the nucleotide sequences of the present application, and the peptides they express, form a unique group of protein types. On the contrary, putative peptides derived from the nucleotide sequences of the application have various functions assigned to them purely on the basis of their similarity to known proteins.

The applicant has grouped the polynucleotides of the application into activity categories according to putative functions of the proteins they encode. However, the applicants' groupings do not form a homogenous set of proteins either in structure or function. For example Seq IDs 3 and 5 are directed toward enzymes that may affect production of flavour compounds. However, these enzymes have unrelated activities; Seq ID 3 encodes a histidinol-phosphate aminotransferase, whereas Seq ID 5 encodes a cysteine desulfurase which are unrelated reactions. Seq ID 15 encodes a heat shock protein which belongs to a totally different class of compounds those involved in production of flavour compounds.

In the absence of a common structure and/or specific biological activity existing between the proteins encoded by the polynucleotides claimed, there are no special technical features identified in the specification which unite the claimed inventions.

The ISA therefore considers that each nucleotide/peptide sequence pair (defined in Table 1 pages 14 - 21) comprises one invention and that there are 59 different inventions (the inventions being numbered sequentially).

However, as a service to the applicants, the ISA will search the first ten inventions, which comprises 10 nucleotide and 10 protein sequences, without inviting additional search fees.

The ISA is also prepared, for a single additional search fee, to search any further group of ten inventions that the applicant may nominate. If the applicants wish all sequences to be searched, they will be required to pay five additional search fees.

This offer should not be taken to have any bearing on the ISA's assessment of the number of inventions claimed in the present application.